

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYALEPT safely and effectively. See full prescribing information for MYALEPT.

MYALEPT® (metreleptin) for injection for subcutaneous use
Initial U.S. Approval: 2014

WARNING: RISK OF ANTI-METRELEPTIN ANTIBODIES WITH NEUTRALIZING ACTIVITY AND RISK OF LYMPHOMA

See full prescribing information for complete boxed warning.

Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with MYALEPT. The consequences are not well characterized but could include inhibition of endogenous leptin action and loss of MYALEPT efficacy. Worsening metabolic control and/or severe infection have been reported.

Test for anti-metreleptin antibodies with neutralizing activity in patients with severe infections or loss of efficacy during MYALEPT treatment. Contact Aegerion Pharmaceuticals, Inc. at 1-866-216-1526 for neutralizing antibody testing. (4.1, 5.1)

T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with MYALEPT. Carefully consider the benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. (5.2)

MYALEPT is available only through a restricted program called the MYALEPT REMS PROGRAM. (5.3)

- Males greater than 40 kg body weight: starting dose 2.5 mg/day, increase or decrease by 1.25 mg to 2.5 mg/day to a maximum dose of 10 mg/day. (2.1)
- Females greater than 40 kg body weight: starting dose 5 mg/day, increase or decrease by 1.25 mg to 2.5 mg/day to a maximum dose of 10 mg/day. (2.1)

----- DOSAGE FORMS AND STRENGTHS -----

MYALEPT is supplied as a sterile, white, solid, lyophilized cake of 11.3 mg metreleptin per vial to deliver 5 mg per mL when reconstituted in 2.2 mL of BWFI or WFI. (3)

----- CONTRAINDICATIONS -----

- General obesity not associated with congenital leptin deficiency. (4.1)
- Hypersensitivity to metreleptin. (4.2)

----- WARNINGS AND PRECAUTIONS -----

- Anti-metreleptin antibodies with neutralizing activity: Could inhibit endogenous leptin action and/or result in loss of MYALEPT efficacy. Test for neutralizing antibodies in patients with severe infections or loss of efficacy during MYALEPT treatment. (5.1)
- T-cell lymphoma: Carefully consider benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. (5.2)
- Hypoglycemia: A dose adjustment, including possible large reductions, of insulin or insulin secretagogue may be necessary. Closely monitor blood glucose in patients on concomitant insulin or insulin secretagogue therapy. (5.4)
- Autoimmunity: Autoimmune disorder progression has been observed in patients treated with MYALEPT. Carefully consider benefits and risks of MYALEPT treatment in patients with autoimmune disease. (5.5)
- Hypersensitivity: Hypersensitivity reactions (e.g., anaphylaxis, urticaria or generalized rash) have been reported. Patient should promptly seek medical advice regarding suspected reactions. (5.6)
- Benzyl Alcohol Toxicity: Preservative-free sterile WFI recommended for neonates and infants. (5.7)

----- ADVERSE REACTIONS -----

Most common in clinical trials (≥10%): headache, hypoglycemia, decreased weight, abdominal pain. (5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aegerion Pharmaceuticals, Inc. at 1-855-303-2347 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- USE IN SPECIFIC POPULATIONS -----

- Pregnancy: MYALEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No adequate and well-controlled studies have been conducted with metreleptin in pregnant women. (8.1)
- Nursing Mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2015

----- INDICATIONS AND USAGE -----

MYALEPT is a leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. (1)

Limitations of Use

- The safety and effectiveness of MYALEPT for the treatment of complications of partial lipodystrophy have not been established. (1)
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established. (1)
- MYALEPT is not indicated for use in patients with HIV-related lipodystrophy. (1)
- MYALEPT is not indicated for use in patients with metabolic disease, without concurrent evidence of generalized lipodystrophy. (1)

----- DOSAGE AND ADMINISTRATION -----

Administer as a subcutaneous injection once daily after the lyophilized cake is reconstituted with Bacteriostatic Water for Injection (BWFI) or preservative-free sterile Water for Injection (WFI). (2.1)

The recommended daily dosages are:

- Body weight 40 kg or less: starting dose 0.06 mg/kg/day, increase or decrease by 0.02 mg/kg to a maximum daily dose of 0.13 mg/kg. (2.1)

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANTI-METRELEPTIN ANTIBODIES WITH NEUTRALIZING ACTIVITY AND RISK OF LYMPHOMA

Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with MYALEPT. The consequences of these neutralizing antibodies are not well characterized but could include inhibition of endogenous leptin action and/or loss of MYALEPT efficacy. Severe infection and/or worsening metabolic control have been reported. Test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of MYALEPT efficacy during treatment. Contact Aegerion Pharmaceuticals, Inc. at 1-866-216-1526 for neutralizing antibody testing of clinical samples [see *Contraindications (4.1) and Warnings and Precautions (5.1)*].

T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with MYALEPT. Carefully consider the benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy [see *Warnings and Precautions (5.2)*].

Because of these risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the risk for lymphoma, MYALEPT is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MYALEPT REMS PROGRAM [see *Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

1.1 Patients with Generalized Lipodystrophy

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.

Limitations of Use

- The safety and effectiveness of MYALEPT for the treatment of complications of partial lipodystrophy have not been established.
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including nonalcoholic 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

See Table 1 for the recommended daily dose and maximum recommended daily dose in adults and pediatric patients.

Based on clinical response (e.g., inadequate metabolic control) or other considerations (e.g., tolerability issues, excessive weight loss [especially in pediatric patients]), MYALEPT dosage may be decreased or increased to the maximum dosage listed in Table 1.

Table 1: MYALEPT Recommended Dosage

| Baseline Weight | Starting Daily Dose (injection volume) | Dose Adjustments (injection volume) | Maximum Daily Dose (injection volume) |
|---------------------------|--|--------------------------------------|---------------------------------------|
| Males and Females ≤ 40 kg | 0.06 mg/kg (0.012 mL/kg) | 0.02 mg/kg (0.004 mL/kg) | 0.13 mg/kg (0.026 mL/kg) |
| Males > 40 kg | 2.5 mg (0.5 mL) | 1.25 mg (0.25 mL) to 2.5 mg (0.5 mL) | 10 mg (2 mL) |
| Females > 40 kg | 5 mg (1 mL) | 1.25 mg (0.25 mL) to 2.5 mg (0.5 mL) | 10 mg (2 mL) |

MYALEPT should be administered once daily at the same time every day. MYALEPT can be administered any time of day without regard to the timing of meals.

Instruct patients that if a dose is missed, administer the dose as soon as noticed, and resume the normal dosing schedule the next day.

2.2 MYALEPT Preparation and Storage

Healthcare practitioners should provide proper training to patients and caregivers regarding how to prepare and administer the correct dose of MYALEPT prior to self-use. The patients and caregivers should prepare and administer the first dose of MYALEPT under

the supervision of a qualified healthcare professional.

Instruct patients to store the vials of lyophilized powder in their carton in the refrigerator as soon as received [see *How Supplied/Storage and Handling (16.2)*].

MYALEPT can be reconstituted aseptically with 2.2 mL of sterile Bacteriostatic Water for Injection (BWFI), USP (0.9% benzyl alcohol), or with 2.2 mL of sterile Water for Injection (WFI).

When reconstituted in BWFI, MYALEPT solution can be used within 3 days when stored in the refrigerator between 36°F and 46°F (2°C and 8°C) and protected from light [see *How Supplied/Storage and Handling (16.2)*]. Discard unused reconstituted solution after 3 days. Attach the supplied sticker to the vial and enter the discard date.

For use in neonates and infants, reconstitute with preservative-free sterile WFI [see *Warnings and Precautions (5.7) and Use in Specific Populations (8.4)*]. When reconstituted in sterile WFI, MYALEPT should be administered immediately. Unused reconstituted solution cannot be saved for later use and should be discarded.

Reconstitution of the Lyophilized Powder

Instruct patients to follow the directions below for reconstitution of the lyophilized powder:

- Remove the vial containing the MYALEPT lyophilized powder from the refrigerator and allow the vial to warm to room temperature prior to use.
- Visually inspect the vial containing MYALEPT. The cake of lyophilized powder should be intact and white in color.
- Using a 3-mL syringe with a 22-gauge or smaller diameter needle withdraw 2.2 mL of sterile Bacteriostatic Water for Injection (BWFI) or preservative-free sterile Water for Injection (WFI). Do not reconstitute MYALEPT with other diluents.
- Inject the BWFI or WFI into the vial containing the lyophilized powder of MYALEPT, slowly injecting down the side of the vial. It is normal for some bubbles to form.
- Remove the needle and syringe from the vial and **gently swirl** the contents to reconstitute. **Do not shake or vigorously agitate.** When properly mixed, the MYALEPT reconstituted solution should be clear and free of clumps or dry powder, bubbles or foam. Do not use the solution if discolored or cloudy, or if particulate matter remains.
- Regarding the compatibility of MYALEPT reconstituted solution with other solutions:
 - Do not mix with, or transfer into, the contents of another vial of MYALEPT.
 - Do not add other medications, including insulin. Use a separate syringe for insulin injections.

See the MYALEPT Instructions for Use for complete administration instructions. The instructions can also be found at www.mylept.com.

2.3 Administration Instructions

Healthcare practitioners should instruct patients and caregivers on the proper subcutaneous injection technique with care to avoid intramuscular injection in patients with minimal subcutaneous adipose tissue. Never administer MYALEPT intravenously or intramuscularly.

Instruct patients to follow the recommended injection technique:

- Using a 1-mL syringe with a needle appropriate for subcutaneous injection, withdraw the prescribed dose of MYALEPT reconstituted solution.
- Remove any large air pockets or large bubbles from the filled syringe prior to administration. Some small bubbles may remain in the syringe.
- Administer MYALEPT into the subcutaneous tissue of the abdomen, thigh or upper arm. Advise patients to use a different injection site each day when injecting in the same region. After choosing an injection site, pinch the skin and at a 45-degree angle, inject the MYALEPT reconstituted solution subcutaneously. Avoid intramuscular injection, especially in patients with minimal subcutaneous adipose tissue.
- Doses exceeding 1 mL can be administered as two injections (the total daily dose divided equally) to minimize potential injection-site discomfort due to injection volume. When dividing doses due to volume, doses can be administered one after the other.

Do not mix MYALEPT with insulin. Use a separate syringe for each medication. If MYALEPT and insulin are administered at the same time of day, they may be injected in the same body area using two different injection sites.

See the MYALEPT Instructions for Use for complete administration instructions. The instructions can also be found at www.mylept.com.

2.4 Dosage Adjustments of Medications Known to Cause Hypoglycemia

Dosage adjustments, including possible large reductions, of insulin or insulin secretagogue (e.g., sulfonylurea) may be necessary in some patients to minimize the risk of hypoglycemia [see *Warnings and*

Precautions (5.4) and Adverse Reactions (6.1)]. Closely monitor blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogue (e.g., sulfonylurea) when treating with MYALEPT.

2.5 Discontinuation in Patients at Risk for Pancreatitis

When discontinuing MYALEPT therapy in patients with risk factors for pancreatitis (e.g., history of pancreatitis, severe hypertriglyceridemia), tapering of the dose over a one-week period is recommended. During tapering, monitor triglyceride levels and consider initiating or adjusting the dose of lipid-lowering medications as needed. Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 11.3 mg of metreleptin supplied in a vial as a sterile, white, solid, lyophilized cake (delivers 5 mg per mL of metreleptin when reconstituted with 2.2 mL of BWFI or WFI).

4 CONTRAINDICATIONS

4.1 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 [see *Warnings and Precautions (5.1)*].

4.2 Hypersensitivity

MYALEPT is contraindicated in patients with prior severe hypersensitivity reactions to metreleptin or to any of the product components. Known hypersensitivity reactions have included anaphylaxis, urticaria and generalized rash [see *Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Development of Antibodies that Neutralize Endogenous Leptin and/or MYALEPT

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), and in three patients without lipodystrophy who received MYALEPT in clinical studies (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. Test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of MYALEPT efficacy during treatment. Contact Aegerion Pharmaceuticals, Inc. at 1-866-216-1526 for neutralizing antibody testing of clinical samples [see *Adverse Reactions (6.2)*].

5.2 Lymphoma

Three cases of T-cell lymphoma have been reported in the MYALEPT lipodystrophy program; all three patients had 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.

Lymphoproliferative disorders, including lymphomas, have been reported in patients with acquired generalized lipodystrophy not treated with MYALEPT. A causal relationship between MYALEPT treatment and the development and/or progression of lymphoma has not been established. Acquired lipodystrophies are associated with autoimmune disorders, and autoimmune disorders are associated with an increased risk of malignancies including lymphomas.

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

5.3 MYALEPT REMS Program

MYALEPT is available only through a restricted distribution program under a REMS, called the MYALEPT REMS Program, because of the risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the risk for lymphoma [see *Warnings and Precautions (5.1, 5.2)*].

Notable requirements of the MYALEPT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.

- Pharmacies must be certified with the program and only dispense MYALEPT after receipt of the MYALEPT REMS Prescription Authorization Form for each new prescription.

Further information is available at www.myaleptrems.com or 1-855-6MYALEPT.

5.4 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Dosage adjustments, including possible large reductions, of insulin or insulin secretagogue (e.g., sulfonylurea) may be necessary in some patients to minimize the risk of hypoglycemia [see *Dosage and Administration (2.4) and Adverse Reactions (6.1)*]. Closely monitor blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogue (e.g., sulfonylurea), when treating with MYALEPT.

5.5 Autoimmunity

Leptin plays a role in immune system homeostasis. Acquired lipodystrophies are associated with autoimmune disorders including autoimmune hepatitis and membranoproliferative glomerulonephritis. Cases of progression of autoimmune hepatitis and membranoproliferative glomerulonephritis (associated with massive proteinuria and renal failure) were observed in some patients with acquired generalized lipodystrophy treated with MYALEPT. A causal relationship between MYALEPT treatment and the development and/or progression of autoimmune disease has not been established. The potential benefits and risks of MYALEPT treatment should be carefully considered in patients with autoimmune disease.

5.6 Hypersensitivity

There have been reports of generalized hypersensitivity (e.g., anaphylaxis, urticaria or generalized rash) in patients taking MYALEPT. If a hypersensitivity reaction occurs, instruct the patient to promptly seek medical advice regarding discontinuation of MYALEPT.

5.7 Benzyl Alcohol Toxicity

MYALEPT contains benzyl alcohol when reconstituted with BWFI. MYALEPT contains no preservative when reconstituted with sterile Water for Injection (WFI). Preservative-free WFI is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death in pediatric patients, particularly in neonates and premature infants [see *Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Open-Label, Single-Arm Study

The safety of MYALEPT was evaluated in 48 patients with generalized lipodystrophy in a single-arm, open-label study [see *Clinical Studies (14.1)*]. The median duration of exposure in this trial was 2.7 years with a range of 3.6 months to 10.9 years. The most frequent adverse reactions are summarized in Table 2.

Table 2: Adverse Reactions of 5% or Greater Incidence in Patients with Generalized Lipodystrophy Receiving MYALEPT in an Open-Label, Single-Arm Study

| | All Subjects N=48 (%) | | All Subjects N=48 (%) |
|---------------------------|-----------------------|-----------------------------------|-----------------------|
| Headache | 6 (13) | Ovarian cyst | 4 (8) |
| Hypoglycemia ¹ | 6 (13) | Upper respiratory tract infection | 4 (8) |
| Decreased weight | 6 (13) | Anemia | 3 (6) |
| Abdominal pain | 5 (10) | Back pain | 3 (6) |
| Arthralgia | 4 (8) | Diarrhea | 3 (6) |
| Dizziness | 4 (8) | Paresthesia | 3 (6) |
| Ear infection | 4 (8) | Proteinuria | 3 (6) |
| Fatigue | 4 (8) | Pyrexia | 3 (6) |
| Nausea | 4 (8) | | |

1. Hypoglycemic events were assessed as mild, moderate, severe, or life threatening based on the protocol specified definitions: Mild: Documentation of low plasma glucose values with no symptoms; Moderate: Presence of clinical symptoms requiring ingestion of glucose, self-alleviated; Severe: Presence of neuroglycopenic symptoms requiring assistance from others for alleviation; Life threatening: Loss of consciousness and/or requiring intervention by administration of intravenous glucose or intramuscular glucagon.

In patients with generalized lipodystrophy receiving MYALEPT in this study, less common adverse reactions included injection-site erythema and urticaria (N=2 [4%]).

Six patients (13%) had 7 adverse reactions of hypoglycemia, 6 of which occurred in the setting of concomitant insulin use, with or without oral antihyperglycemic agents.

Two patients (4%) had events of pancreatitis, both of whom had a medical history of pancreatitis.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Anti-metreleptin antibodies were detected in 84% (36/43) of generalized lipodystrophy patients studied in the MYALEPT trials. Total anti-metreleptin antibody titers ranged between 1:5 and 1:1,953,125. The incompleteness of the current immunogenicity database precludes understanding of the magnitude and persistence of the observed anti-drug antibody responses. Anti-metreleptin 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 with generalized lipodystrophy tested. Adverse events reported in these two patients included severe infections and worsening of metabolic control (increases in HbA1c and/or triglycerides). Test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of MYALEPT efficacy during treatment. Contact Aegerion Pharmaceuticals, Inc. at 1-866-216-1526 for testing of clinical samples.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. The immunogenicity assays utilized in clinical trials lacked sensitivity, resulting in potential underestimation of the number of samples positive for anti-metreleptin antibodies with neutralizing activity. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to metreleptin with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug interaction studies were performed.

Leptin is a cytokine and may have the potential to alter the formation of cytochrome P450 (CYP450) enzymes. This should be taken into account when prescribing concomitant drugs metabolized by CYP450 (e.g., oral contraceptives and drugs with a narrow therapeutic index). The effect of metreleptin on CYP450 enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of MYALEPT, in patients being treated with these types of agents, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the agent adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There is a program that monitors outcomes in women exposed to MYALEPT during pregnancy. Women who become pregnant during MYALEPT treatment are encouraged to enroll. Patients or their physicians should call 1-855-6MYALEPT to enroll.

Risk Summary

There are no adequate and well-controlled studies of MYALEPT in pregnant women. All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations and 15% to 20% for pregnancy loss. In a pre- and postnatal development study in mice, administration of metreleptin caused prolonged gestation and dystocia resulting in maternal death during parturition and lower survival of offspring in the immediate postnatal period at doses starting approximately at the maximum recommended clinical dose. Because animal reproduction studies are not always predictive of human response, MYALEPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-Associated Maternal and Fetal Risk

The contribution of MYALEPT to obstetrical risks and complications is unknown compared with those already documented in the lipodystrophy patient population (e.g., gestational diabetes, macrosomia, eclampsia, intrauterine growth retardation, intrauterine death, and miscarriage).

Labor and Delivery

The effects of MYALEPT on labor and delivery in pregnant women are unknown. In an in vitro study of human myometrial tissue exposed to a recombinant leptin, human uterine contractility was inhibited. Furthermore, prolonged gestation and dystocia were observed in animal studies with metreleptin (see below).

Animal Data

Metreleptin administered to pregnant mice during the period of organogenesis was not teratogenic at doses ranging between 7- and 15-fold the maximum recommended clinical dose, based on body surface area of a 20- and 60-kg patient, respectively.

In a pre- and postnatal development study in mice, metreleptin administered at doses of 3, 10, and 30 mg/kg (approximately 1-, 5-, and 15-fold the clinical dose for a 60-kg subject, based on body surface area) from gestation day 6 to lactation day 21 caused prolonged gestation and dystocia at all doses, starting at approximately the maximum recommended clinical dose. Prolonged gestation resulted in the death of some females during parturition and lower survival of offspring within the immediate postnatal period. Consistent with metreleptin pharmacology, decreased maternal body weight was observed from gestation throughout lactation at all doses and resulted in reduced weight of offspring at birth, which persisted into adulthood. However, no developmental abnormalities were observed and reproductive performance of the first or second generations was not affected at any dose.

Placental transfer of metreleptin into the fetus was low (approximately 1%) following subcutaneous dosing.

8.3 Nursing Mothers

It is not known if MYALEPT is present in human milk. Endogenous leptin is present in human milk. Because of the potential for serious adverse reactions (including possible adverse reactions related to passage of anti-metreleptin antibodies) in nursing infants from MYALEPT a decision should be made whether to discontinue nursing or discontinue the drug, taking into account importance of drug to the mother [see Adverse Reactions (6.2) and Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The MYALEPT study included a total of 35 pediatric patients (73%) with an age range from 1 to 17 years [see Clinical Studies (14.1)]. No clinically meaningful differences were observed in the efficacy and safety of MYALEPT between pediatric and adult patients.

MYALEPT contains benzyl alcohol when reconstituted with BWFI. MYALEPT contains no preservative when reconstituted with WFI. Preservative-free WFI is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome," the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources. When reconstituted with 2.2 mL of BWFI, MYALEPT contains 1.76 mg of benzyl alcohol per mg of metreleptin or 9 mg of benzyl alcohol per mL of reconstituted product.

8.5 Geriatric Use

Clinical trials of MYALEPT did not include sufficient numbers of subjects aged 65 and over (n=1) to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There were no reports of overdose in the lipodystrophy clinical trial program of MYALEPT. In the event of an overdose, patients should be monitored and appropriate supportive treatment be initiated as dictated by the patient's clinical status.

11 DESCRIPTION

MYALEPT (metreleptin) for injection is a recombinant human leptin analog for injection that binds to and activates the leptin receptor. Metreleptin (recombinant methionyl-human leptin) is produced in *E. coli* and differs from native human leptin by the addition of a methionine residue at its amino terminus. Metreleptin is a 147-amino acid, nonglycosylated, polypeptide with one disulfide bond between Cys-97 and Cys-147 and a molecular weight of approximately 16.15 kDa.

MYALEPT is supplied as a sterile, white, solid, lyophilized cake containing 11.3 mg that is reconstituted with 2.2 mL of BWF1 or WFI to a final formulation of 5 mg/mL metreleptin for subcutaneous injection. Inactive ingredients are: glutamic acid (1.47 mg/mL), glycine (20 mg/mL), polysorbate 20 (0.1 mg/mL), and sucrose (10 mg/mL), pH 4.25.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adipocytes store lipids to meet the fuel requirements of non-adipose tissues during fasting. In patients with generalized lipodystrophy, the deficiency of adipose tissue leads to hypertriglyceridemia and ectopic deposition of fat in non-adipose tissues such as liver and muscle, contributing to metabolic abnormalities including insulin resistance. Native leptin is a hormone predominantly secreted by adipose tissue that informs the central nervous system of the status of energy stores in the body. In patients with generalized lipodystrophy, leptin deficiency, resulting from the loss of adipose tissue, contributes to excess caloric intake, which exacerbates the metabolic abnormalities.

MYALEPT (metreleptin) for injection exerts its function by binding to and activating the human leptin receptor (ObR), which belongs to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway.

12.2 Pharmacodynamics

Clinical studies in patients with generalized lipodystrophy suggest that MYALEPT increases insulin sensitivity and reduces food intake. Improvements in insulin sensitivity and reductions in food intake are consistent with lower HbA1c, fasting glucose, and fasting triglyceride values that were seen in the MYALEPT clinical trial [see *Clinical Studies (14)*].

12.3 Pharmacokinetics

There are limited data on the pharmacokinetics of metreleptin in patients with generalized lipodystrophy, and therefore, no formal exposure-response analysis has been performed. It should be noted that the leptin assay measures both endogenous leptin as well as exogenously administered metreleptin.

Absorption

Peak serum leptin concentration (C_{max}) occurred approximately 4.0 to 4.3 hours after subcutaneous administration of single doses ranging from 0.1 to 0.3 mg/kg in healthy subjects. In a supportive trial in lipodystrophy patients, the median T_{max} of metreleptin was 4 hours (range: 2 to 8 hours; N=5) following single-dose administration of metreleptin.

Distribution

In studies of healthy adult subjects, following intravenous administration of metreleptin, leptin volume of distribution was approximately 4 to 5 times plasma volume; volumes (V_z) (mean \pm SD) were 370 ± 184 mL/kg, 398 ± 92 mL/kg, and 463 ± 116 mL/kg for 0.3, 1.0, and 3.0 mg/kg/day doses, respectively.

Metabolism and Elimination

No formal metabolism studies have been conducted with metreleptin. Nonclinical data indicate renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation. Following single subcutaneous doses of 0.01 to 0.3 mg/mL metreleptin in healthy subjects, the half-life was 3.8 to 4.7 hours. The clearance of metreleptin is expected to be delayed in the presence of leptin antibodies [see *Adverse Reactions (6.2)*].

Drug Interactions

No drug interaction studies have been conducted in lipodystrophy patients [see *Drug Interactions (7)*].

Specific Populations

Renal Impairment

No formal pharmacokinetic studies were conducted in patients with renal impairment. Nonclinical data indicate renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation. Hence, the pharmacokinetics of metreleptin may be altered in subjects with renal impairment.

Hepatic Impairment

No formal pharmacokinetic studies were conducted in patients with hepatic impairment.

Age, Gender, Race, Body Mass Index

Specific clinical studies have not been conducted to assess the effect of age, gender, race, or body mass index on the pharmacokinetics of metreleptin in patients with generalized lipodystrophy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in rodents have not been conducted with metreleptin. No proliferative or preneoplastic lesions were observed in mice or dogs following treatment up to six months. However, leptin is reported in the literature to promote cell proliferation in vitro and tumor progression in some mouse models of cancer.

Metreleptin was not mutagenic in the Ames bacterial mutagenicity assay or clastogenic in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and human peripheral blood lymphocytes. Metreleptin was not mutagenic or clastogenic in an *in vivo* mouse micronucleus assay.

In a fertility study in mice, metreleptin had no adverse effects on mating, fertility, or early embryonic development at doses ranging between 7 and 15 times the maximum recommended clinical dose based on body surface area of a 20- and 60-kg patient, respectively.

14 CLINICAL STUDIES

14.1 Open-Label, Single-Arm Study

An open-label, single-arm study evaluated MYALEPT treatment in patients with congenital or acquired generalized lipodystrophy and diabetes mellitus, hypertriglyceridemia, and/or increased fasting insulin.

Baseline Disease Characteristics and Demographics

Of the 48 patients enrolled, 32 (67%) had congenital generalized lipodystrophy and 16 (33%) had acquired generalized lipodystrophy. Overall, 36 (75%) patients were female, 22 (46%) were Caucasian, 10 (21%) Hispanic, and 9 (19%) Black. The median age at baseline was 15 years (range: 1 - 68 years), with 35 (73%) patients being less than 18 years of age. The median fasting leptin concentration at baseline was 0.7 ng/mL in males (range: 0.3 - 3.3 ng/mL) and 1.0 ng/mL in females (range: 0.3 - 3.3 ng/mL).

Treatment Duration and Dosage in the Study

The median duration of MYALEPT treatment was 2.7 years (range: 3.6 months - 10.9 years). MYALEPT was administered subcutaneously either once daily or twice daily (in two equal doses). The weighted average daily dose (i.e., the average dose taking into account duration of treatment at different doses) for the 36 patients with baseline body weight greater than 40 kg was 2.6 mg for males and 4.6 mg for females during the first year of treatment, and 3.2 mg for males and 6.3 mg for females over the entire study period. For the 12 patients with baseline body weight less than 40 kg, the weighted average daily dose was 0.06 to 0.11 mg/kg (0.8-4.3 mg) over the entire study period.

Efficacy Results

At baseline, 37 (77%) patients had HbA1c values of 7% or greater, 19 (40%) had HbA1c values of 9% or greater, 33 (69%) had fasting plasma glucose values of 126 mg/dL or greater, 17 (35%) had fasting triglyceride values of 500 mg/dL or greater, and 11 (23%) had fasting triglyceride values of 1000 mg/dL or greater.

Patients treated with MYALEPT had mean/median reductions in HbA1c, fasting glucose, and triglycerides at 1 year (Table 3). The changes in HbA1c, fasting glucose, and triglycerides observed at Month 4 were similar to those at 1 year. Concomitant antihyperglycemic and lipid-altering medication dosage regimens were not held constant during the study; for example, some patients treated with insulin had their dosage increased and others had large reductions or discontinuation of insulin.

Table 3: Results in an Open-Label, Single-Arm Study in Patients with Generalized Lipodystrophy Treated with MYALEPT (N=48)

| Parameter | n | Baseline | Change from Baseline at Month 12 |
|-------------------------------|----|-----------------|----------------------------------|
| | | Mean (SD) | Mean (SD) |
| HbA1c (%) | 35 | 8.5 (2) | -2 (1.5) |
| Fasting Glucose (mg/dL) | 37 | 174 (85) | -49 (75) |
| | | Median (Q1, Q3) | Median Change (Q1, Q3) |
| Fasting Triglycerides (mg/dL) | 36 | 348 (176, 769) | -184 (-643, -21) |
| | | | Median Percent Change (Q1, Q3) |
| | | | -55 (-77, -20)% |

SD = standard deviation; Q = quartile

Among 28 patients with generalized lipodystrophy who had a baseline HbA1c 7% or greater and data available at Month 12, the mean (SD) baseline HbA1c was 9.3 (1.5%) and the mean reduction in HbA1c at Month 12 was 2.4%.

Among 12 patients with generalized lipodystrophy who had a baseline triglyceride level 500 mg/dL or greater and data available at Month 12, the median baseline triglyceride level was 1527 mg/dL and the median reduction in triglycerides at Month 12 was 1117 mg/dL.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- MYALEPT (metreleptin) for injection for subcutaneous administration is supplied in a single carton containing one vial for reconstitution (NDC 76431-210-01).
- Each vial contains 11.3 mg metreleptin (as a sterile, white, solid, lyophilized cake) to deliver 5 mg per mL of metreleptin when reconstituted with 2.2 mL of BWFI or WFI.

16.2 Storage and Handling

- MYALEPT should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C) and protected from light until preparing for use. Keep MYALEPT vials in the carton when not in use.
- MYALEPT should not be used past the expiration date.
- Do not freeze MYALEPT.
- Do not use if the white lyophilized cake is discolored.
- Use with BWFI: when MYALEPT is reconstituted with BWFI, the vial can be used for multiple doses within 3 days when stored in the refrigerator at 36°F to 46°F (2°C to 8°C) and protected from light.
- Use with WFI: when MYALEPT is reconstituted with WFI, the vial can be used for a single dose should be administered immediately. Unused reconstituted solution cannot be saved for later use and should be discarded.
- After reconstitution, the vials should not be frozen (below 0°C) or shaken vigorously. If the reconstituted product is inadvertently frozen, it should be thrown away.
- After reconstitution, the mixture should be clear and colorless. Do not use if visible particulates are present in the solution.
- Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (Medication Guide).

Risk of Neutralizing Antibodies

Advise patients that neutralizing antibodies may result in loss in activity of endogenous leptin or loss of efficacy of MYALEPT. Advise patients on symptoms or signs that would warrant antibody testing [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)].

Risk of Lymphoma

Advise patients that lymphoma has been reported in patients both treated and not treated with MYALEPT. Advise patients on symptoms or signs that indicate changes in hematologic status and the importance of routine laboratory assessments and physician monitoring [see Warnings and Precautions (5.2)].

Risk of Hypoglycemia

Advise patients that the risk of hypoglycemia is increased when MYALEPT is used in combination with insulin or an insulin secretagogue (e.g., sulfonylurea). Explain the symptoms, treatment, and conditions that predispose to development of hypoglycemia to the patient. Advise patients who are taking concomitant insulin, especially those on high doses, or an insulin secretagogue, to closely monitor blood glucose. Hypoglycemia management should be reviewed and reinforced when initiating MYALEPT therapy, particularly when concomitantly administered with insulin or an insulin secretagogue [see Warnings and Precautions (5.4)].

Risk of Autoimmune Disease

Advise patients that worsening of autoimmune disease has been reported during the clinical study of MYALEPT. Advise patients with a history of autoimmune disease on symptoms or signs that indicate exacerbation of underlying autoimmune disease and the importance of routine laboratory assessments and physician monitoring [see Warnings and Precautions (5.5)].

Risk of Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have been reported during use of MYALEPT. If symptoms of hypersensitivity reactions occur, patients should seek medical advice [see Warnings and Precautions (5.6)].

Nursing Mothers

Advise nursing mothers that breastfeeding is not recommended with MYALEPT use [see Use in Specific Populations (8.3)].

Instructions

- Inform patients that each vial of MYALEPT requires reconstitution with BWFI or preservative-free WFI, and administration as subcutaneous injection using a syringe and needle. Injections can be given at any time of the day, with or without meals.
- Patients and caregivers should receive proper training in how to prepare and administer the correct dose of MYALEPT prior to self-administration. The first dose of MYALEPT should be administered by the patient or caregiver under the supervision of a qualified healthcare professional.
- Advise patients on injection technique, dosing regimen, and the importance of proper storage of MYALEPT. Care should be taken to avoid intramuscular injection, especially in patients with minimal subcutaneous adipose tissue.
- Advise patients to read the Instructions for Use for complete administration instructions. The MYALEPT Medication Guide and Instructions for Use should be reviewed before starting therapy and each time the prescription is refilled.
- When discontinuing MYALEPT in patients with a history of pancreatitis and/or severe hypertriglyceridemia, instruct patients to taper their dose over a one-week period. Advise patients that additional monitoring of triglyceride levels and possible initiation or dose adjustment of lipid-lowering medications may be considered [see Dosage and Administration (2.5)].

Manufactured for:

Aegerion[®]
Pharmaceuticals

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