BlueCross BlueShield of Alabama

Myalept® (metreleptin) Prior Authorization

Program Summary

This program applies to Commercial, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Myalept (metreleptin) prior authorization criteria is to ensure that patients prescribed therapy are appropriately selected according to Food and Drug Administration (FDA) product labeling and/or clinical studies. Metreleptin will be initially approved for use in a patient who: a) has been diagnosed with congenital (CGL) or acquired generalized lipodystrophy (AGL). Also, b) the prescriber must be a specialist (e.g. endocrinologist) or has consulted with a specialist, c) the prescriber has drawn baseline HbA_{1C}, triglycerides, and fasting insulin levels prior to beginning metreleptin therapy, d) the patient has an additional diagnosis of diabetes mellitus, hypertriglyceridemia and/or high fasting insulin, e) the patient has failed lifestyle modification and will continue with lifestyle modification during Myalept therapy, and f) the patient has failed maximum tolerable dosing of a conventional agent used for the additional diagnosis. Finally, g) dosing is restricted to FDA labeled dosing and h) the patient must not have a FDA labeled contraindication to therapy with metreleptin. Renewal criteria also requires the prescriber to be a specialist or consult with a specialist. Additionally, the patient must have reduction in HbA_{1C}, triglycerides, and/or fasting insulin from baseline and the patient must continue with lifestyle modification during Myalept therapy. Dosing and contraindication restrictions are the same as initial criteria. Requests for metreleptin will be reviewed when patient-specific documentation is provided.

TARGET DRUGS

Myalept® (metreleptin)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Myalept will be approved when ALL of the following are met:

1. The patient has a diagnosis of either congenital generalized lipodystrophy (CGL) or acquired generalized lipodystrophy (AGL)
   AND
2. The prescriber is a specialist in the area of the patient's disease (e.g. endocrinologist, cardiologist) or the prescriber has consulted with a specialist in the area of the patient's disease
   AND
3. The prescriber has drawn baseline values for HbA_{1C}, triglycerides, and fasting insulin prior to beginning Myalept (metreleptin) therapy
   AND
4. The patient also has at least one of the following additional diagnosis: diabetes mellitus, hypertriglyceridemia (≥200 mg/dL), and/or high fasting insulin (≥30µU/mL)
   AND
5. The patient has failed lifestyle modification (diet modification and exercise) and will continue with lifestyle modification during Myalept (metreleptin) therapy
   AND
6. The patient has failed maximum tolerable dosing of a conventional agent for the additional diagnosis
   AND

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7. The patient does not have any FDA labeled contraindication(s) to therapy with Myalept (metreleptin)
   AND
8. The dose is within FDA labeled dosing guidelines

Length of Approval: 12 months

Renewal Evaluation
Myalept will be approved when ALL of the following are met:
1. The patient has been previously approved through the Prime Therapeutics PA process
   AND
2. The prescriber is a specialist in the area of the patient's disease (e.g. endocrinologist, cardiologist) or the prescriber has consulted with a specialist in the area of the patient's disease
   AND
3. The patient has had a reduction in at least one of the following parameters: HbA_{1C}, triglycerides and/or fasting insulin
   AND
4. The patient will continue with lifestyle modification (i.e. diet and exercise) during therapy with Myalept (metreleptin)
   AND
5. The patient does not have any FDA labeled contraindication(s) to therapy with Myalept (metreleptin)
   AND
6. The dose is within the FDA labeled dose

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

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FDA APPROVED INDICATIONS AND DOSAGE[1]

FDA INDICATION: Metreleptin 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.

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

DOSING:
The recommended daily dosages in milligrams (mg) per kilogram (kg) of body weight are:
- Body weight ≤40 kg: starting dose 0.06 mg/kg/day, increase or decrease by 0.02 mg/kg. Maximum daily dose is 0.13 mg/kg.
- Males >40 kg body weight: starting dose 2.5 mg/day, increase or decrease by 1.25 mg to 2.5 mg/day. Maximum dose is 10 mg/day.
- Females >40 kg body weight: starting dose 5 mg/day, increase or decrease by 1.25 mg to 2.5 mg/day. Maximum dose is 10 mg/day.

Metreleptin should be administered at the same time every day and can be administered any time of the day without regard to meals.

CLINICAL RATIONALE[1-5]

Congenital and acquired generalized lipodystrophy are conditions in which patients are either born with little to no subcutaneous adipose (fat) tissue or are born with normal levels of adipose tissue, but lose adipose tissue over time. Phenotypically, patients often have prominent muscles and subcutaneous veins, dark velvety pigmentation (acanthosis nigricans), and acromegaloid features such as enlarged hands, feet, and mandible. Patients with lipodystrophy typically have a leptin deficiency. Leptin is a hormone that is secreted by fat cells (adipocytes) and is an important regulator of energy homeostasis, fat, and glucose metabolism. It communicates with the central nervous system regarding the status of energy stores within the body. Low leptin levels can lead to excessive caloric intake. Data regarding the range of leptin levels in patients with a confirmed diagnosis of lipodystrophy is limited. Leptin levels may be ordered as a clinical laboratory test; however, neither leptin assays have been standardized nor have normal ranges been well established. A leptin deficiency can often, though not always, result in metabolic, endocrine, and immunological complications. Manifestations of these complications can include insulin resistance/diabetes, high triglycerides, and ectopic lipid distribution in muscle and the liver. These metabolic derangements associated with the lipodystrophy can be severe and may lead to substantial co-morbidities. Some co-morbidities include hepatic cirrhosis/non-alcoholic fatty liver disease, acute pancreatitis, and premature cardiovascular disease. Historically, lipodystrophy has been treated with lifestyle modifications (diet, exercise), use of anti-hyperglycemic medications (metformin, sulfonylureas, thiazolidinediones, insulin), and/or utilization of lipid-lowering medications (fibrates, statins). Due to the substantial insulin resistance and the severity of these metabolic abnormalities, it is difficult to treat them even with the highest doses of the afore-mentioned treatments.

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Congenital generalized lipodystrophy (CGL) or Berardinelli-Seip syndrome is an autosomal recessive disorder characterized by a generalized lack of adipose tissue at birth or shortly after. The disease is not very prevalent; it is estimated that 1 in 10 million people worldwide have the disease. Currently, it is believed that there are at least four gene mutations associated with CGL. Each gene abnormality manifests itself slightly differently than the others in terms of the disease's signs and symptoms. For example, some of type 1 and 2 patients develop bone cysts in the long bones of the arms and legs after puberty, type 2 patients are more often associated with mild to moderate intellectual disability, type 3 patients often have vitamin D abnormalities and type 4 patients many times will have muscular dystrophy, cardiac arrhythmias and/or experience sudden death.

Acquired generalized lipodystrophy (AGL), also known as Lawrence syndrome, is a disorder in which patients are born with normal fat distribution but lose fat in a generalized fashion usually starting in childhood or adolescence. AGL is three times more common in women than in men. Progressive fat loss usually occurs over a period of months to years and affects large areas of the body, especially the face and extremities. It is believed that AGL is caused by panniculitis (inflammation of the fat/subcutaneous inflammatory nodules), autoimmune diseases and/or it may follow infections such as varicella, measles, etc. In many cases, however, the etiology of the disease is unknown.

EFFICACY[1,5]
Metreleptin functions by binding to and activating the human leptin receptor which studies suggest causes an increase in insulin sensitivity and a reduction in food intake.

The efficacy of metreleptin was evaluated in an open label single arm study of 48 patients with congenital (n=32) or acquired generalized (n=16) lipodystrophy who also had at least one of the metabolic abnormalities (diabetes mellitus, hypertriglyceridemia >200 mg/dL, and/or increased fasting insulin (≥30µU/mL). Key exclusion criteria included: human immunodeficiency virus (HIV) infection, infectious liver disease, and acquired lipodystrophy with hematologic abnormalities. 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. The metreleptin treatment duration was 3.6 months to 10.9 years (median = 2.7 years) and metreleptin was administered either once or twice daily. At year 1, patients treated with metreleptin had mean/median reductions in HbA1c (-2%), fasting glucose (-49 mg/dL), and triglycerides (-55%). Concomitant anti-hyperglycemic and lipid-altering medications dosing regimens were not held constant throughout the study.

SAFETY[1,5]
Metreleptin contains a black box warning for 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 metreleptin. The consequences are not well characterized but could include inhibition of endogenous leptin action and loss of metreleptin 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 metreleptin treatment.
- T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with metreleptin. Carefully consider the benefits and risks of treatment with metreleptin in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy.

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Due to the issues included in the box warning, metreleptin is only available through a restricted REMS program.

Metreleptin is contraindicated in patients with general obesity not associated with congenital leptin deficiency. It has been shown to be ineffective in treating general obesity and the development of anti-metreleptin antibodies with neutralizing activity has been reported in obese patients treated with metreleptin.

REFERENCES

1. Myalept prescribing information. Aegerion Pharmaceuticals, Inc. September 2015.
2. Handelsman Y, Oral EA, Bloomgarden Z. The Clinical Approach To The Detection of Lipodystrophy – An AACE Consensus Statement, *Endocr Pract*. 2013;19(No.1):107-116.
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5. Myalept Dossier. Bristol-Myers Squibb. March 10, 2014.

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