OVERVIEW

Myalept, a recombinant analog of human leptin, is indicated as an adjunct to diet as replacement therapy to treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Generalized lipodystrophy is a rare, “ultra-orphan”, chronic, heterogeneous, and life-threatening disorder in which there is an abnormality of adipose tissue distribution and insufficient fat tissue, which is required for normal metabolic function. Robust epidemiological data are not available; however, approximately 400 cases of generalized lipodystrophy have been reported in the literature. Although there is heterogeneity in the lipodystrophy syndromes, all share the feature of subcutaneous (SC) adipose tissue loss resulting in more severe metabolic abnormalities (e.g., diabetes mellitus and hypertriglyceridemia) than generally noted with obesity. Congenital generalized lipodystrophy (CGL) is an autosomal recessive disorder that is apparent from birth and is associated with loss of adipose tissue affecting the limbs, trunk, face, and neck, accompanied by muscularity and visible SC veins. Acquired generalized lipodystrophy (AGL) may be associated with panniculitis (approximately 25%), autoimmune conditions such as juvenile dermatomyositis, autoimmune hemolytic anemia, and autoimmune hepatitis (approximately 25%), or be idiopathic (approximately 50%). Loss of adipose tissue occurs over weeks to years, often in childhood or adolescence. Partial types of lipodystrophy also exist, with the most common form associated with use of antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection. However, Myalept is not indicated for the treatment of antiretroviral-associated lipodystrophy.

There are serious safety concerns associated with Myalept. Myalept has two Boxed Warnings related to the risk of lymphoma and the risk of development of neutralizing anti-metreleptin antibodies associated with loss of endogenous leptin activity and/or loss of Myalept efficacy. However, a causal relationship between Myalept treatment and lymphoma has not been established. In addition, patients with lipodystrophy and severe hypertriglyceridemia are predisposed to pancreatitis. Pancreatitis was reported in five patients during the pivotal trial of Myalept, however, these events were associated with an interruption of treatment or non-compliance. There have been 10 deaths reported in patients either during or following treatment with Myalept attributed to a variety of causes. The Food and Drug Administration (FDA) safety evaluation of Myalept noted that there were significant safety concerns; however, it is difficult to determine the role Myalept played in the adverse events (AEs) observed in clinical trials. Due to the potential for serious AEs, Myalept is only available through a Risk Evaluation and Mitigation Strategy (REMS) program, which requires practitioners to complete training and utilize a Myalept REMS Prescription Authorization Form for each new Myalept prescription.

In 2013, the American Association of Clinical Endocrinologists (AACE) published a consensus statement aimed to improve the clinical detection of lipodystrophy syndromes. In this document the AACE highlighted the wide variability in the metabolic manifestations and fat loss in patients with lipodystrophy syndromes. Due to the rarity of the condition, and therefore lack of robust evidence, specific guidelines for the treatment of lipodystrophy have not been developed. This consensus statement noted that in patients with severe metabolic abnormalities, conventional treatments (anti-diabetic medications and lipid-lowering drugs), whether used alone or in combination, are unlikely to re-establish metabolic control. In 2012, the National Organization of Rare Disorders released a physician’s guide to lipodystrophy. This document also noted that there are no clinical trials available to direct therapy. The
guide recommends a high carbohydrate, low fat diet, along with traditional medications for lipid abnormalities and diabetes, most commonly metformin, sulfonylureas, and insulin therapy. It states that SC metreleptin replacement therapy has been found to improve diabetes control, hepatic steatosis, and hypertriglyceridemia in markedly hypoleptinemic patients with generalized lipodystrophies, but its’ effect in patients with familial partial lipodystrophy appears to be modest.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Myalept. Because of the specialized skills required for evaluation and diagnosis of patients treated with Myalept, as well as the monitoring required for AEs and long-term efficacy, approval requires Myalept to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Myalept is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Generalized Lipodystrophy (Congenital or Acquired) with complications of leptin deficiency. Approve in patients who meet the following criteria (a, b, and c):
   a) Conventional therapy for metabolic disturbances has failed (e.g. diet and lifestyle modification, statins, anti-diabetic agents)
   b) Myalept is prescribed by or in consultation with an endocrinologist a geneticist physician specialist
   c) The dose will not exceed 0.13 mg/kg/day for patients ≤ 40 kg or 10 mg/day for patients > 40 kg

2. Continuation of therapy - Treatment of complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Approve in patients who meet all of the criteria noted above and the patient’s condition must have improved or stabilized while using Myalept (e.g. evidenced by sustained improvement in triglyceride levels, hemoglobin A1c from baseline, or provider confirmation that Myalept is still working)

Dosing

Initial Dosing: ≤40 kg 0.06 mg/kg once daily increase or decrease by 0.02 mg/kg daily based on response or adverse effects or >40 kg 2.5 mg (males) or 5 mg (females) once daily; increase or decrease by 1.25-2.5 mg daily based on response or adverse effects

Extended Dosing: maximum dose 0.13 mg/kg once daily (patient ≤40 kg) or 10mg once daily (patient >40 kg)

Approval Duration

Approval = 365 days

Conditions Not Recommended for Approval

The safety and efficacy of Myalept has not been established for the following conditions. Myalept will not be approved for these indications:

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1. Treatment of general obesity not associated with congenital leptin deficiency.
2. Treatment of liver disease, including nonalcoholic steatohepatitis (NASH)
3. Treatment of complications of partial lipodystrophy
4. Treatment of HIV-related lipodystrophy
5. Treatment of metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of generalized lipodystrophy

REFERENCES

Data on file, Myalept™ Product Dossier: Based on AMCP guidelines for formulary submission, version 2.1. Bristol-Myers Squibb/Astra-Zeneca; received March 26, 2014.

