VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Myalept® (metreleptin for subcutaneous injection – Aegerion)

TAC APPROVAL DATE: 09/12/2018

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.[1] Limitations of Use: The safety and efficacy of Myalept have not been established for the treatment of complications of partial lipodystrophy, liver disease (including nonalcoholic steatophepatitis [NASH], human immunodeficiency virus (HIV)-related lipodystrophy, or metabolic disease without concurrent evidence of generalized lipodystrophy.

Disease Overview

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.[2] Robust epidemiological data are not available. Approximately 400 cases of generalized lipodystrophy have been reported in the literature.[2-3] A recent publication estimates the prevalence of all types of lipodystrophy to be between 1.3 and 4.7 cases per million based on available literature, with the prevalence of generalized lipodystrophy estimated to be much lower at approximately 0.23 cases per million.[24] 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.[4-5] 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.[3,5,7] 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%).[3,5] 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 HIV infection. However, Myalept is not indicated for the treatment of antiretroviral-associated lipodystrophy.

Guidelines

Guidelines on the diagnosis and management of lipodystrophy syndromes were published in 2016 and endorsed by multiple groups of endocrine experts, including the Endocrine Society, the Pediatric Endocrine Society, the American Diabetes Association, and the American Association of Clinical Endocrinologists.[7] These guidelines note that lipodystrophy is an incurable condition and no treatment will regrow adipose tissue. Myalept is the only drug specifically indicated for the treatment of lipodystrophy. Myalept, along with diet, is recommended as the first-line treatment for metabolic and endocrine abnormalities in patients with generalized lipodystrophy (Class I, Level B). In children, Myalept may also be used to prevent the development of comorbidities (Class IIb, Level C). While not FDA-approved for use in patients with partial lipodystrophy, the guidelines state that Myalept may be used in this setting, if the patient is hypoleptinemic (leptin < 4 ng/mL) and has a glycosylated hemoglobin (HbA1c) > 8% and/or triglycerides > 500 mg/dL (Class IIb, Level B); although it is noted that response to Myalept therapy is less robust in partial lipodystrophy than in generalized lipodystrophy. In one study,

Myalept improved blood glucose regulation in the guideline-recommended partial lipodystrophy population; in a second study it demonstrated improved insulin sensitivity and triglycerides. However, in another study, Myalept did not demonstrate improvement in glycemic parameters in patients with familial partial lipodystrophy and serum leptin < 7 ng/mL. Other recommendations are provided for the management of specific comorbidities associated with lipodystrophy syndromes (e.g., diabetes, dyslipidemia, hypertension, liver disease).

Safety

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.[1] However, a causal relationship between Myalept treatment and lymphoma has not been established. At the time of its initial FDA-approval, there had been 10 deaths reported in patients either during or following treatment with Myalept attributed to a variety of causes.[6] The FDA safety evaluation of Myalept in 2013 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.

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 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Generalized Lipodystrophy (Congenital or Acquired):** Approve Myalept for 3 years in patients with generalized lipodystrophy if the medication is prescribed by, or in consultation with, an endocrinologist or a geneticist physician specialist.

   Myalept is indicated to treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.[1] Myalept is not indicated for other conditions, such as partial lipodystrophy, liver disease (including nonalcoholic steatohepatitis [NASH]), HIV-related lipodystrophy, or metabolic disease not related to generalized lipodystrophy. There are serious safety concerns with Myalept, including risk for lymphoma (Boxed Warning), the development of neutralizing antibodies (Boxed Warning), hypoglycemia, and autoimmune disorder progression. Patients should be monitored throughout treatment for development of serious AEs. In the professional opinion of specialist physicians, this criterion has been adopted.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Myalept has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **General Obesity not associated with Congenital Leptin Deficiency:** Myalept is contraindicated in patients with general obesity not associated with congenital leptin deficiency.[1] Myalept was previously evaluated in two clinical development programs for obesity, both as monotherapy (n > 1,100) and in combination with Symlin® (pramlintide acetate for injection; n > 600).[4] Published studies on the effects of leptin therapy in these patients without leptin deficiency yielded conflicting efficacy results.[8-9] The studies involving obese patients (some with type 2 diabetes mellitus), with the exception of one dose-escalation trial, failed to show significant weight loss with Myalept therapy and resulted in clinically insignificant changes in other metabolic parameters, such as insulin sensitivity.[10-14] One additional randomized, double-blind, placebo-controlled crossover study evaluated the efficacy of leptin administration to promote further weight reduction in patients who had undergone Roux-en-Y gastric bypass surgery.[20] Following 16 weeks of therapy, Myalept was not found to promote additional decreases in body weight compared with placebo.

2. **Human Immunodeficiency Virus (HIV)-related Lipodystrophy.** Myalept is not indicated for the treatment of patients with HIV-related lipodystrophy.[1] Results from four small studies of patients with HIV-associated lipodystrophy and leptin deficiency showed mixed results with Myalept therapy.[15-18] One study found significantly improved fasting insulin levels, insulin resistance and high-density lipoprotein (HDL) levels, but no significant differences in fasting glucose levels, free-fatty acid levels, or low-density lipoprotein (LDL) levels when Myalept was compared with placebo.[15] Another demonstrated improved fasting insulin levels, but no difference in intravenous glucose disappearance, fasting serum glucose concentration, glycosylated hemoglobin (HbA_{1C}) levels, body mass index (BMI), or lipid parameters after treatment with Myalept.[16] Two additional studies found that therapy with Myalept improved some, but not all metabolic parameters in patients infected with HIV.[17-18] More information is needed to determine if Myalept is a safe and effective treatment for HIV-related lipodystrophy.

3. **Partial Lipodystrophy.** The safety and efficacy of Myalept in the treatment of the complications of partial lipodystrophy have not been established.[1] The effects of Myalept therapy in patients with partial lipodystrophy have been evaluated; the pivotal trial of Myalept included a subset of patients (n = 24) with partial lipodystrophy.[19] Overall, patients with partial lipodystrophy had milder baseline metabolic abnormalities than patients with generalized lipodystrophy. Following 12 months of Myalept therapy, patients experienced a reduction in HbA_{1C}, fasting plasma glucose, and fasting triglycerides; however, the magnitude of the improvements was less than those observed in patients with generalized lipodystrophy. Additional data also highlight the heterogeneity of partial lipodystrophy; Myalept may provide improvement in some metabolic parameters in certain patients with partial lipodystrophy, but more data are needed to confirm these benefits.[21-23] Current lipodystrophy guidelines (2016) outline certain patients with partial lipodystrophy that may benefit from Myalept therapy, but indicate a lower level of evidence to support use in this patient population compared with generalized lipodystrophy.[7] Myalept prescribing information continues to list partial lipodystrophy as a limitation of use.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual Revision	No changes to criteria.	07/15/2015
Annual Revision	No changes to criteria.	08/03/2016
Annual Revision	No changes to criteria.	08/23/2017
Annual Revision	No changes to criteria.	09/12/2018

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.