MEDICAL MUTUAL®

Drug Policy

Policy: **CC**	**Myalept (metreleptin)** **Prior Authorization Policy**	**Annual Review Date:** **09/19/2024** **Last Revised Date:** **09/19/2024**

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.[2-3] 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.[6] 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

This policy involves the use of Myalept. Prior authorization is recommended for pharmacy benefit coverage of Myalept. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval**

for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Myalept as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Myalept be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy 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).** Approve for duration noted if the patient meets ALL of the following criteria (A, B, C, D, and E):

   A) Patient meets ONE of the following (i or ii):
   - **i.** Patient has **congenital** generalized lipodystrophy and meets ONE of the following criteria (a or b):
     - **a)** Patient has had a genetic test demonstrating one gene mutation (i.e., AGPAT2, BSCL2, CAV1, or PTRF) confirming the diagnosis of congenital generalized lipodystrophy; OR
     - **b)** Patient meets BOTH of the following criteria (1 and 2):
       - **(1)** Patient has had a genetic test that did not demonstrate an AGPAT2, BSCL2, CAV1, or PTRF gene mutation; AND
       - **(2)** A clinical diagnosis of congenital generalized lipodystrophy has been made by a specialist with experience in treating patients with lipodystrophy; OR
   - **ii.** Patient has **acquired** generalized lipodystrophy; AND

   B) Patient has experienced one or more manifestations of leptin deficiency; AND
   Note: Manifestations of leptin deficiency include hyperinsulinemia, type 2 diabetes mellitus, and hypertriglyceridemia.

   C) Myalept will be used in conjunction with dietary modification; AND

   D) Conventional therapy for metabolic disturbances has failed (e.g. diet and lifestyle modification, statins, anti-diabetic agents); AND

   E) Medication is prescribed by or in consultation with an endocrinologist or a geneticist

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 has 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).

Initial Approval/ Extended Approval.
A) *Initial Approval:* 1 year
B) *Extended Approval:* 1 year

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. (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).[3] Published studies on the effects of leptin therapy in these patients without leptin deficiency yielded conflicting efficacy results.[4,5] 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.[6-10] 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.[11] Following 16 weeks of therapy, Myalept was not found to promote additional decreases in body weight compared with placebo.

2. Liver disease, including nonalcoholic steatohepatitis (NASH).

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.[16] 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. There are data showing sustained improvements out to 36 months as well.[17] 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.[18-20] 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.[2] Myalept prescribing information continues to list partial lipodystrophy as a limitation of use.

4. **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.[12-15] 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.[12] 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.[13] Two additional studies found that therapy with Myalept improved some, but not all metabolic parameters in patients infected with HIV.[14,15] More information is needed to determine if Myalept is a safe and effective treatment for HIV-related lipodystrophy.

5. Metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of generalized lipodystrophy.

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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