Drug and Biologic Coverage Policy

Effective Date 9/15/2023
Next Review Date… 9/15/2024
Coverage Policy Number IP0340

Metreleptin

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for metreleptin subcutaneous injection (**Myalept®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Metreleptin (Myalept) is considered medically necessary when the following are met:

1. **Generalized Lipodystrophy (Congenital or Acquired).** Individual meets **ALL** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Congenital generalized lipodystrophy and meets **ONE** of the following:
         a. Has had a genetic test demonstrating one gene mutation (i.e., *AGPAT2*, *BSCL2*, *CAV1*, or *PTRF*) confirming the diagnosis of congenital generalized lipodystrophy

b. Has had a genetic test that does not demonstrate an *AGPAT2*, *BSCL2*, *CAV1*, or *PTRF* gene mutation AND a clinical diagnosis of congenital generalized lipodystrophy has been made by a specialist with experience in treating individuals with lipodystrophy

ii. Acquired generalized lipodystrophy diagnosis

B. Has one or more complications of leptin deficiency (for example, type 2 diabetes mellitus, hypertriglyceridemia, hyperinsulinemia)

C. Myalept will be used as an adjunct to dietary modification

D. Medication is prescribed by, or in consultation with, an endocrinologist or a geneticist physician specialist

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When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Metreleptin (Myalept) is considered medically necessary for continued use when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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. **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.[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.

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.[1]

Background

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 (including diabetes mellitus and hypertriglyceridemia) without concurrent evidence of generalized lipodystrophy.

Congenital generalized lipodystrophy is an inherited autosomal recessive disease.[21] *AGPAT2* and *BSCL2* gene mutations responsible for 95% of currently identified cases, while mutations of *CAV1* and the *PTRF* gene have also been reported, although much less frequently. Several patients with congenital generalized lipodystrophy do not have any of the four known gene mutations, indicating that not all mutations associated with congenital generalized lipodystrophy have been identified. Patients with this condition can experience a variety of complications, such as hyperinsulinemia, diabetes mellitus, hypertriglyceridemia, pancreatitis, fatty liver, and loss of subcutaneous adipose tissue.

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.[2] 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. In children, Myalept may also be used to prevent the development of comorbidities.

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