

PRIOR AUTHORIZATION POLICY

- POLICY:** Lipodystrophy – Myalept Prior Authorization Policy
- Myalept® (metreleptin for subcutaneous injection – Aegerion)

REVIEW DATE: 10/21/2020

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 steatoph hepatitis [NASH], human immunodeficiency virus (HIV)-related lipodystrophy, or metabolic disease (including diabetes mellitus and hypertriglyceridemia) 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

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.

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 adverse events 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 the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Myalept is not recommended in the following situations:

- 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. There are data showing sustained improvements out to 36 months as well.²⁵ 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.

REFERENCES

1. Myalept[®] for injection [prescribing information]. Cambridge, MA: Aegerion Pharmaceuticals, Inc.; May 2020.
2. Chou K, Perry CM. Metreleptin: first global approval. *Drugs*. 2013;73(9):989-997.
3. Handelsman Y, Oral EA, Bloomgarden ZT, et al. The clinical approach to the detection of lipodystrophy – an AACE consensus statement. *Endocr Pract*. 2013;19:107-116.
4. Bristol-Myers Squibb and AstraZeneca. Metreleptin (BLA STN125390). Briefing document for the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee. Meeting Date: December 11, 2013. Available at: <https://wayback.archive-it.org/7993/20170403223914/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm331504.htm>. Accessed on: September 24, 2020.
5. Huang-Doran I, Sleight A, Rochford JJ, et al. Lipodystrophy: metabolic insights from a rare disorder. *J Endocrinol*. 2010;207(3):245-255.
6. Myalept (metreleptin). Presented at: the Food and Drug Administration (FDA) Advisory Committee Meeting; December 11, 2013. Available at: <https://wayback.archive-it.org/7993/20170403223914/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm331504.htm>. Accessed on September 24, 2020.
7. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *J Clin Endocrinol Metab*. 2016;101(12):4500-4511.
8. Zelissen PM, Stenlof K, Lean ME, et al. Effect of three treatment schedules of recombinant methionyl human leptin on body weight in obese adults: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2005;7(6):755-761.
9. Ravussin E, Smith SR, Mitchell JA, et al. Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. *Obesity (Silver Spring)*. 2009;17(9):1736-1743.
10. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA*. 1999;282(16):1568-1575.
11. Hukshorn CJ, van Dielen FM, Buurman WA, et al. The effect of pegylated recombinant human leptin (PEG-OB) on weight loss and inflammatory status in obese subjects. *Int J Obes Relat Metab Disord*. 2002;26(4):504-509.
12. Mittendorfer B, Horowitz JF, DePaoli AM, et al. Recombinant human leptin treatment does not improve insulin action in obese subjects with type 2 diabetes. *Diabetes*. 2011;60:1474-1477.
13. Moon HS, Matarese G, Brennan AM, et al. Efficacy of metreleptin in obese patients with type 2 diabetes: cellular and molecular pathways underlying leptin tolerance. *Diabetes*. 2011;60:1647-1656.
14. Shetty GK, Matarese G, Magkos F, et al. Leptin administration to overweight and obese subjects for six months increases free leptin concentrations but does not alter circulating hormones of the thyroid and IGF axes during weight loss induced by a mild hypocaloric diet. *Eur J Endocrinol*. 2011;165(2):249-254.
15. Lee JH, Chan JL, Sourlas E, et al. Recombinant methionyl human leptin therapy in replacement doses improves insulin resistance and metabolic profile in patients with lipoatrophy and metabolic syndrome induced by the highly active antiretroviral therapy. *J Clin Endocrinol Metab*. 2006;91(7):2605-2611.
16. Magkos F, Brennan A, Sweeney L, et al. Leptin replacement improves postprandial glycemia and insulin sensitivity in human immunodeficiency virus-infected lipoatrophic men treated with pioglitazone: a pilot study. *Metabolism*. 2011;60(7):1045-1049.

17. Mulligan K, Khatami H, Schwarz JM, et al. The effects of recombinant human leptin on visceral fat, dyslipidemia, and insulin resistance in patients with human immunodeficiency virus-associated lipodystrophy and hypoleptinemia. *J Clin Endocrinol Metab.* 2009;94(4):1137-1144.
18. Sekhar RV, Jahoor F, Iyer D, et al. Leptin replacement therapy does not improve the abnormal lipid kinetics of hypoleptinemic patients with HIV-associated lipodystrophy syndrome. *Metabolism.* 2012;61(10):1395-1403.
19. 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.
20. Korner J, Controy R, Febres G, et al. Randomized double-blind placebo-controlled study of leptin administration after gastric bypass. *Obesity (Silver Spring).* 2013;21(5):951-956.
21. Ajluni N, Dar M, Xu J, et al. Efficacy and safety of metreleptin in patients with partial lipodystrophy: lessons from an expanded access program. *J Diabetes Metab.* 2016;7(3):659.
22. Simha V, Subramanyam L, Szczepaniak L, et al. Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the Dunnigan variety. *J Clin Endocrinol Metab.* 2012;97(3):785-792.
23. Diker-Cohen T, Cochran E, Gorden P, et al. Partial and generalized lipodystrophy: comparison of baseline characteristics and response to metreleptin. *J Clin Endocrinol Metab.* 2015;100(5):1802-1810.
24. Chiquette E, Oral EA, Garg A, et al. Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. *Diabetes Metab Syndr Obes.* 2017;10:375-383.
25. Oral EA, Gorden P, Cochran E, et al. Long-term effectiveness and safety of metreleptin in the treatment of patients with partial lipodystrophy. *Endocrine.* 2019;64(3):500-511.