



**Medication Policy Manual**

**Policy No:** dru344

**Topic:** Myalept™, metreleptin

**Date of Origin:** June 20, 2014

**Committee Approval Date:** October 13, 2017

**Next Review Date:** October 2018

**Effective Date:** November 1, 2017

### **IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

### **Description**

Metreleptin (Myalept™) is a subcutaneously injected self-administered recombinant leptin analog that is used to treat the metabolic complications associated with leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Complications include hyperglycemia and hyperlipidemia.

## Policy/Criteria

I. Most contracts require prior authorization approval of metreleptin prior to coverage. Metreleptin may be considered medically necessary when criteria A through D below are met.

A. A diagnosis of congenital generalized lipodystrophy or acquired generalized lipodystrophy (also known as Berardinelli-Seip syndrome or Lawrence syndrome, respectively) with hyperglycemia and/or hyperlipidemia.

**AND**

B. If hyperglycemia is present, treatment with at least one of the following medications was ineffective, unless all are contraindicated, not tolerated, or not indicated.

1. metformin
2. a sulfonylurea
3. an insulin
4. a thiazolidinedione

**AND**

C. If hyperlipidemia is present, treatment with a statin was ineffective, contraindicated, not tolerated, or not indicated.

**AND**

D. There is clinical documentation that lifestyle modifications (such as diet and exercise) have been addressed.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers metreleptin to be a self-administered medication.

B. When prior authorization is approved, metreleptin may be authorized in quantities of up to 30 vials per 30 days.

C. Authorization shall be reviewed at least every 6 months to confirm that current medical necessity criteria are met and that the medication is effective.

III. Metreleptin is considered not medically necessary when used for partial lipodystrophy.

IV. Metreleptin is considered investigational when used for all other conditions, including but not limited to:

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

B. HIV-related lipodystrophy.

C. Metabolic disease (e.g. diabetes mellitus, hypertriglyceridemia) without concurrent evidence of congenital or acquired generalized lipodystrophy.

## Position Statement

- Metreleptin is a self-administered recombinant leptin analog, indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Complications include hyperglycemia and hyperlipidemia.
- Congenital and acquired lipodystrophy are exceedingly rare, with approximately 1,350 cases reported in literature. The prevalence of congenital forms is estimated to be less than one in a million births. [1]
- Patients enrolled in clinical trials for metreleptin also received concurrent conventional medications such as metformin and insulin to control hyperglycemia and statins to control hyperlipidemia.
- The American Association of Clinical Endocrinologists suggest lifestyle modifications and treatment with conventional antihyperglycemic and lipid-lowering medications as therapy options for congenital and acquired generalized lipodystrophy. [2]
- The safety and effectiveness of metreleptin for the treatment of complications of partial lipodystrophy have not been established. Unlike generalized lipodystrophy, partial lipodystrophy is more heterogenous in presentation with varying degrees of subcutaneous adipose tissue loss. Also, there is not a defined and reliable leptin level threshold that correlates with improvement in complications associated with partial lipodystrophy.
- The safety and effectiveness of metreleptin for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established.
- Metreleptin is not indicated for use in patients with HIV-related lipodystrophy.
- Metreleptin is not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy.
- Metreleptin has a boxed warning and REMS program in place regarding the risk of development of neutralizing antibodies and T-cell lymphoma.
- The recommended dosage of metreleptin is dependent on gender and weight. The maximum daily dose for any gender or weight is 10 mg. Metreleptin is available in vials, each containing 11 mg of metreleptin after reconstitution.

### *Clinical Efficacy*

#### CONGENITAL OR ACQUIRED GENERALIZED LIPODYSTROPHY

- Generalized lipodystrophy is a condition characterized by diffuse loss of subcutaneous adipose tissue (with resultant leptin deficiency) and associated with substantial morbidity and mortality due to complications from metabolic abnormalities and/or serious co-morbidities typically associated with these syndromes. [1]
- Generalized lipodystrophy differs from partial lipodystrophy in the clinical presentation and degree of metabolic abnormalities. Partial lipodystrophy is more heterogenous in presentation with varying degrees of subcutaneous adipose tissue loss. [1]

- The efficacy of metreleptin was evaluated in two unpublished, open-label, single-arm trials in 72 total patients with congenital or acquired lipodystrophy and associated metabolic complications, such as increased blood glucose and triglycerides. [1]
- At 1 year, patients treated with metreleptin had reductions in hemoglobin A1C (mean change -1.4%), fasting glucose (mean change -42 mg/dL), and triglycerides (median change -32% mg/dL). The most significant changes were observed in patients with generalized lipodystrophy. [1]
- Use of concomitant antidiabetic medications (e.g. metformin, insulin) and lipid-modifying medications (e.g. statins) were permitted during the clinical trials. Thus, reported treatment effects may not be entirely attributable to metreleptin.
- A1C, blood glucose, and triglycerides are considered surrogate markers. The effect of metreleptin on long-term cardiovascular morbidity and mortality is unknown.
- The American Association of Clinical Endocrinologists suggest the following therapeutic options in the treatment of congenital or acquired generalized lipodystrophy: [2]
  - \* Treatment with antihyperglycemics (such as metformin, sulfonylureas, insulin, and thiazolidinediones).
  - \* Treatment with lipid-lowering medications (such as statins).
  - \* Lifestyle modifications (such as diet and exercise).

## PARTIAL LIPODYSTROPHY

- Unlike generalized lipodystrophy, partial lipodystrophy is more heterogenous in presentation with varying degrees of subcutaneous adipose tissue loss. With partial lipodystrophy, there is not a defined and reliable leptin level threshold that correlates with improvement in complications associated with partial lipodystrophy. [1]
- The FDA Endocrinologic and Metabolic Drugs Advisory Committee strongly recommended against approval of metreleptin for partial lipodystrophy citing lack of substantial evidence for efficacy for this population. Additional concerns included the heterogeneity of the clinical presentation and the lack of established criteria to define the disease. [1]
- One small observational study of 14 patients with familial partial lipodystrophy of the Dunnigan variety (FPLD) did not show a statistical difference in the primary endpoint of change in fasting serum triglycerides. [3]
- One ongoing clinical trial of 55 patients (36 with generalized lipodystrophy and 19 with partial lipodystrophy) showed reductions in glycemic variables (such as A1C), triglycerides, and liver enzymes (ALT and AST), but these results are preliminary. [4]
- The FDA approved prescribing information for metreleptin states that it should not be used for the treatment of complications of partial lipodystrophy, as safety and effectiveness has not been established in this setting. [5]

## LIVER DISEASE, INCLUDING NONALCOHOLIC STEATOHEPATITIS (NASH)

- The FDA Endocrinologic and Metabolic Drugs Advisory Committee strongly recommended against approval of metreleptin for hepatic steatosis. They noted that hepatic steatosis is not a severe enough diagnosis to warrant treatment with metreleptin and there was no data presented to support the changes observed in liver-related parameters as being clinically important. [1]
- The FDA approved prescribing information for metreleptin states that it should not be used for the treatment of liver disease, including NASH, as safety and effectiveness has not been established in this setting. [5]

## HIV-RELATED LIPODYSTROPHY

- One small pilot study of 9 HIV-positive men with clinical evidence of lipoatrophy and low leptin concentrations were placed on pioglitazone treatment and randomized to receive either metreleptin (n = 5) or placebo (n = 4) for 3 months. Results showed patients who received metreleptin had improved postprandial glycemia and insulin sensitivity, but need to be confirmed in larger, well-controlled clinical trials. [6]
- The FDA approved prescribing information for metreleptin states that it is not indicated for use in patients with HIV-related lipodystrophy. [5]

## METABOLIC DISEASE WITHOUT CONCURRENT EVIDENCE OF CONGENITAL OR ACQUIRED GENERALIZED LIPODYSTROPHY

- Two small trials of obese or overweight patients without lipodystrophy demonstrated that treatment with metreleptin did not alter body weight compared to placebo. [7,8]
- The FDA approved prescribing information for metreleptin states that it is not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy. [5]

### *Safety*

- Metreleptin has a boxed warning and REMS program in place regarding the risk of development of neutralizing antibodies and T-cell lymphoma. The REMS program requires both prescriber and pharmacy certification. [5]
- The most common adverse drug reactions (incidence  $\geq 10\%$ ) to metreleptin reported in clinical trials were headache, hypoglycemia, decreased weight, and abdominal pain. [5]

### *Dosing Considerations* [5]

- For males and females less than or equal to 40 kg, the starting daily dose is 0.06 mg/kg, and the maximum daily dose is 0.13 mg/kg.
- For males greater than 40 kg, the starting daily dose is 2.5 mg, and the maximum daily dose is 10 mg.
- For females greater than 40 kg, the starting daily dose is 5 mg, and the maximum daily dose is 10 mg.

- Each vial contains 11.3 mg metreleptin (as sterile, white, solid, lyophilized cake) to deliver 5 mg per mL of metreleptin when reconstituted with 2.2 mL of bacteriostatic water for injection or sterile water for injection.

Cross References
None

Codes	Number	Description
N/A		

### References

1. Endocrinologic and Metabolic Drugs Advisory Committee Drug Approval Package: Myalept (metreleptin) BLA 125390. [cited 8/31/2017]; Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2014/125390Orig1s000TOC.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125390Orig1s000TOC.cfm)
2. Handelsman, Y, Oral, EA, Bloomgarden, ZT, et al. The clinical approach to the detection of lipodystrophy - an AACE consensus statement. *Endocr Pract.* 2013;19:107-16. PMID: 23435042
3. 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;97:785-92. PMID: 22170723
4. Chan, JL, Lutz, K, Cochran, E, et al. Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. *Endocr Pract.* 2011;17:922-32. PMID: 22068254
5. Myalept™ [package insert]. Princeton, NJ: Bristol-Myers Squibb; February 2014
6. 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;60:1045-9. PMID: 21081243
7. 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;60:1647-56. PMID: 21617185
8. Shetty, GK, Matarese, G, Magkos, F, et al. Leptin administration to overweight and obese subjects for 6 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;165:249-54. PMID: 21602313

### Revision History

Revision Date	Revision Summary
10/13/2017	No criteria changes with this annual update.
06/10/2016	No Criteria Changes