Original Effective Date: 09/2019
Current Effective Date: 07/04/2024
Last P&T Approval/Version: 04/30/2025
Next Review Due By: 04/2026
Policy Number: C17341-A

Myalept (metreleptin)

PRODUCTS AFFECTED

Myalept (metreleptin subcutaneous injection)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Congenital or acquired generalized lipodystrophy

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. GENERALIZED LIPODYSTROPHY WITH COMPLICATION OF LEPTIN DEFICIENCY:
1. Documented diagnosis of congenital (e.g., Berardinelli-Seip syndrome) or acquired (e.g., Lawrence syndrome) generalized lipodystrophy associated with leptin deficiency
AND

2. Documentation of confirmed leptin deficiency as measured by Linco assay obtained after an overnight fast:
   a. Females: Circulating leptin levels <12 ng/mL
   b. Males: Circulating leptin levels <8 ng/mL
   c. Children (6 months – 5 years): Circulating leptin levels <6 ng/mL

   AND
3. Documentation demonstrates the member has at least ONE of the following:
   a. Diabetes mellitus or insulin resistance with persistent hyperglycemia (HgA1c>7%) despite both of the following: Dietary intervention AND Optimized insulin therapy at maximum tolerated doses

      OR
   b. Persistent hypertriglyceridemia (TG >250mg/dL) despite both of the following: Dietary intervention AND Optimized therapy with at least two triglyceride-lowering agents from different classes (e.g. statins, fibrates) at maximum tolerated doses

   AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Myalept (metreleptin) include: General obesity not associated with congenital leptin deficiency, Hypersensitivity to metreleptin.]

CONTINUATION OF THERAPY:

A. GENERALIZED LIPODYSTROPHY WITH COMPLICATION OF LEPTIN DEFICIENCY:

1. Documentation of positive clinical response to therapy (e.g., improved glycemic control, decrease in hepatic enzyme levels, sustained improvement in triglyceride levels, or decrease in hemoglobin A1c from baseline)

   AND
2. Documentation that member continues on optimized hyperglycemia or hypertriglyceridemia treatment regimen

   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization:12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with an endocrinologist or geneticist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests (if available)]

AGE RESTRICTIONS:

No restriction

QUANTITY:

Maximum dose is 10 mg/day (1 vial) (See Appendix)

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Subcutaneous

DRUG CLASS:
Leptin analog

FDA-APPROVED USES:
Indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy

Limitations of Use:
- *The safety and effectiveness of Myalept for the treatment of complications of partial lipodystrophy have not been established.*
- *The safety and effectiveness of Myalept for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established.*
- *Myalept is not indicated for use in patients with HIV-related lipodystrophy.*
- *Myalept in not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital or acquired generalized lipodystrophy*

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Table 1: Myalept Recommended Dosage

Baseline Weight	Starting daily dose (inj volume)	Dose adjustments (inj volume)	Maximum daily dose (inj volume)
≤40kg (male and female)	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Males >40kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Females >40kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

Table 2: Example Dosing Chart for Patients Less than or Equal to 40 kg

Weight	Starting Dose	Dose Adjustment	Maximum Dose
5 kg	0.30 mg (0.06 mL or 6 Units)	0.10 mg (0.02 mL or 2 Units)	0.65 mg (0.13 mL or 13 Units)
10 kg	0.60 mg (0.12 mL or 12 Units)	0.20 mg (0.04 mL or 4 Units)	1.3 mg (0.26 mL or 26 Units)
15 kg	0.90 mg (0.18 mL or 18 Units)	0.30 mg (0.06 mL or 6 Units)	1.95 mg (0.39 mL or 39 Units)
20 kg	1.2 mg (0.24 mL or 24 Units)	0.40 mg (0.08 mL or 8 Units)	2.6 mg (0.52 mL or 52 Units)
25 kg	1.5 mg (0.3 mL or 30 Units)	0.50 mg (0.1 mL or 10 Units)	3.25 mg (0.65 mL or 65 Units)
30 kg	1.8 mg (0.36 mL or 36 Units)	0.60 mg (0.12 mL or 12 Units)	3.9 mg (0.78 mL or 78 Units)
35 kg	2.1 mg (0.42 mL or 42 Units)	0.70 mg (0.14 mL or 14 Units)	4.55 mg (0.91 mL or 91 Units)
40 kg	2.4 mg (0.48 mL or 48 Units)	0.80 mg (0.16 mL or 16 Units)	5.2 mg (1.03 mL or 103 Units)

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
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 theliterature.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 In 2013, the American Association of Clinical Endocrinologists (AACE) published a consensus statement aimed to improve the clinical detection of lipodystrophy syndromes. This consensus statement noted that in patients with severe metabolic abnormalities, conventional treatments (anti- diabetic medications and lipid-lowering drugs), whether used alone or in combination, are unlikely to re-establish metabolic control. In 2012, the National Organization of Rare Disorders released a physician's guide to lipodystrophy. The guide recommends a high carbohydrate, low fat diet, along with traditional medications for lipid abnormalities and diabetes, most commonly metformin, sulfonylureas, and insulin therapy. It states that metreleptin (Myalept) replacement therapy has been found to improve diabetes control, hepatic steatosis, and hypertriglyceridemia in markedly hyperleptinemic patients with generalized lipodystrophies, but its' effect in patients with familial partial lipodystrophy appears to be modest. In 2016, The Journal of Clinical Endocrinology & Metabolism released a consensus statement regarding lipodystrophy syndromes. Like the above sources, the statement recommends diet, exercise, and conventional treatments for comorbidities. It also recommends metreleptin (with diet) as first-line treatment for metabolic and endocrine abnormalities in generalized lipodystrophy. Metreleptin may be considered for prevention of these comorbidities in children and is currently the only drug approved specifically for lipodystrophy.

Myalept REMS Program

MYALEPT is available only through a restricted distribution program under a REMS, called the MYALEPT REMS Program, because of the risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin and/or MYALEPT and the risk for lymphoma.
Notable requirements of the MYALEPT REMS Program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Pharmacies must be certified with the program and only dispense MYALEPT after receipt of the MYALEPT REMS Prescription Authorization Form for each new prescription.

Further information is available at www.myaleptrems.com or 1-855-669-2537.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Myalept (metreleptin) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Myalept (metreleptin) include: patients with general obesity not associated with congenital leptin deficiency, hypersensitivity to metreleptin.

OTHER SPECIAL CONSIDERATIONS:
Myalept (metreleptin) has a black box warning for risk of anti-metreleptin antibodies with neutralizing activity and risk of lymphoma.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Myalept SOLR 11.3 mg

REFERENCES

1. Myalept (metreleptin) for injection, for subcutaneous use [prescribing information]. Cary, NC: Chiesi USA, Inc..; March 2024.
2. Rodriguez AJ, Mastronardi CA, Paz-Filho GJ. New advances in the treatment of generalized lipodystrophy: role of metreleptin. Ther Clin Risk Manag. 2015; 11:1391-1400.
3. Handelsman Y, Oral AE, Bloomgarden ZT, et al. The clinical approach to the detection of lipodystrophy – an AACE consensus statement. Endocr Pract. 2013;19:107-116.
4. Chan JL, Lutz K, Cochran E, et al. Clinical effects of long-term metreleptin treatment in patients with lipodystrophy. Endocr Pract. 2011;17:922-932.
5. The physician's guide to lipodystrophy disorders. The National Organization for Rare Disorders website. Released in 2012. Accessed on July 9, 2019.
6. Rebecca J. Brown, David Araujo-Vilar, Pik To Cheung, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 12, 1 December 2016, Pages 4500–4511.
7. Chan JL, Lutz K, Cochran E, et al. Clinical effects of long-term metre-leptin treatment in patients with lipodystrophy. Endocr Pract. 2011;17(6):922–932.
8. Rodriguez AJ, Mastronardi CA, Paz-Filho GJ. New advances in the treatment of generalized lipodystrophy: role of metreleptin. Ther Clin Risk Manag. 2015;11:1391–1400.
9. De Ferranti, S. D., Steinberger, J., Ameduri, R., Baker, A., Gooding, H., Kelly, A. S., Zaidi, A. N. (2019). Cardiovascular risk reduction in high-risk pediatric patients: A scientific statement from the American Heart Association. Circulation, 139(13). Doi:10.1161/cir.0000000000000618

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Continuation of Therapy References	Q2 2025
REVISION- Notable revisions: Required Medical Information	Q2 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity FDA-Approved Uses Appendix Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Duration of Approval Prescriber Requirements	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file