BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 4/1/19
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MYALEPT® (metreleptin) subcutaneous injection

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

MYALEPT® (metreleptin) subcutaneous injection (cont.)

Criteria:

MYALEPT IS AVAILABLE ONLY THROUGH RESTRICTED DISTRIBUTION UNDER A RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM CALLED MYALEPT REMS PROGRAM.

- **Criteria for initial therapy:** Myalept (metreleptin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in or is in consultation with an Endocrinologist
2. Individual is 1 year of age or older
3. A confirmed diagnosis of leptin deficiency in a patient with congenital or acquired generalized lipodystrophy and **BOTH** of the following:
    - Type 2 diabetes mellitus (DM) or insulin resistance with persistent HgA1C > 7 despite dietary intervention, metformin, and other therapy for DM
    - Persistent hypertriglyceridemia levels (> 250 mg/dL) despite dietary intervention and optimal therapy with at least **two** triglyceride lowering agents from different classes (fibrate, omega-3 fatty acid, statin)
4. A fasting leptin concentration at baseline is below the normal range (lab result must be submitted)
5. Individual continues a low-fat diet to treat the complications of leptin deficiency
6. There is no partial lipodystrophy
7. There is no liver disease, including nonalcoholic steatohepatitis (NASH)
8. There is no HIV-related lipodystrophy
9. There is no metabolic disease, including diabetes mellitus and hypertriglyceridemia without concurrent evidence of congenital or acquired generalized lipodystrophy
10. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    - Blood glucose, HgA1C
    - Triglycerides
11. There are **NO** contraindications
    - Contraindications include:
        - General obesity not associated with leptin deficiency
        - Hyper sensitivity to metreleptin or any of the product components

Initial approval duration: 12 months

MYALEPT® (metreleptin) subcutaneous injection (cont.)

- **Criteria for continuation of coverage (renewal request):** Myalept (metreleptin) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in or is in consultation with an Endocrinologist

  2. Individual's condition responded while on therapy
     - Response is defined as achieved and maintains for **ALL** of the following:
       - At least a 20% reduction in HgA1C over baseline
       - At least a 25% reduction in fasting glucose over baseline
       - At least a 50% reduction in triglycerides over baseline

  3. Individual continues a low-fat diet to treat the complications of leptin deficiency

  4. There is no partial lipodystrophy

  5. There is no liver disease, including nonalcoholic steatohepatitis (NASH)

  6. There is no HIV-related lipodystrophy

  7. There is no metabolic disease, including diabetes mellitus and hypertriglyceridemia without concurrent evidence of congenital or acquired generalized lipodystrophy

  8. Individual has been adherent with the medication

  9. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
     - Contraindications as listed in the criteria for initial therapy section
     - Significant adverse effect such as:
       - Anti-metreleptin antibodies with neutralizing activity
       - T-lymphoma
       - Severe infection
       - Severe hypoglycemia

  Renewal duration: 12 months

- Myalept for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

MYALEPT® (metreleptin) subcutaneous injection (cont.)

These indications include, *but are not limited to*:

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Description:

Myalept (metreleptin) is a recombinant human leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in individuals with generalized lipodystrophy (congenital or acquired). Metreleptin binds to and activates the leptin receptor. Generalized lipodystrophy is a condition associated with a lack of fat tissue and very low leptin levels, a hormone made by fat tissue.

Lipodystrophy is accompanied by other hormonal abnormalities and is often accompanied by metabolic derangements, including insulin resistance, diabetes mellitus, hepatic steatosis or steatohepatitis, and dyslipidemia. In addition, fat may be deposited in other areas such as in the liver and muscle. Hyperglycemia and hypertriglyceridemia that are resistant to treatment or the use of very high doses of insulin may be important clues of lipodystrophy in the clinical setting.

Adipocytes store lipids to meet the fuel requirements of non-adipose tissues during fasting. In patients with generalized lipodystrophy, the deficiency of adipose tissue leads to hypertriglyceridemia and ectopic deposition of fat in liver and muscle, contributing to metabolic abnormalities including insulin resistance. Native leptin is a hormone predominantly secreted by adipose tissue that informs the central nervous system of the status of energy stores in the body. In patients with generalized lipodystrophy, leptin deficiency, resulting from the loss of adipose tissue, contributes to excess caloric intake, which exacerbates the metabolic abnormalities.

There are four major subtypes of lipodystrophy: congenital generalized lipodystrophy (CGL), acquired generalized lipodystrophy (AGL), familial partial lipodystrophy (FPL), and acquired partial lipodystrophy (APL). Human immunodeficiency virus-associated lipodystrophy has been categorized as a type of APL.

Individuals with CGL are born with little or no fat tissue over their entire body. CGL is also known as Berardinelli-Seip syndrome, is an autosomal recessive disorder. Individuals with AGL are born with normal fat distribution but lose fat tissue over time, starting in childhood or adolescence. There is a progressive loss of fat affecting the whole body including palms and soles. AGL is also known as Lawrence syndrome.

Therapeutic options for the metabolic management of lipodystrophy consist of lifestyle modifications (diet and exercise), conventional anti-hyperglycemic and lipid-lowering medications, and leptin replacement therapy. Metformin, sulfonylureas (glyburide, glipizide, and others), thiazolidinediones (pioglitazone, rosiglitazone), and insulin can be used to manage hyperglycemia, while fibrates, omega-3 fatty acids, and/or statins can be used to manage hypertriglyceridemia. Myalept (metreleptin) is used as leptin replacement therapy, in addition to diet, in individuals with CGL or AGL.

Clinical studies in patients with generalized lipodystrophy suggest that metreleptin increases insulin sensitivity and reduces food intake. Improvements in insulin sensitivity and reductions in food intake are consistent with lower HbA1c, fasting glucose, and fasting triglyceride values that were seen in the clinical trials.

MYALEPT® (metreleptin) subcutaneous injection (cont.)

Myalept (metreleptin) is contraindicated in patients with general obesity not associated with congenital leptin deficiency.

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

Because of the risks associated with the development of neutralizing antibodies and lymphoma, Myalept (metreleptin) is available only through the Myalept Risk Evaluation and Mitigation Strategy (REMS) Program.

Definitions:

Risk Evaluation and Mitigation Strategies (REMS):

Use of Myalept is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks. Under this REMS program, prescribers must be certified with the program by enrolling in 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.

Fibric acid derivatives:

- Choline fenofibrate
- Fenofibrate
- Fenofibric acid
- Gemfibrozil

Omega-3 fatty acids derivatives:

- Lovaza or generic
- Triklo
- Vascepa

Statins:

- Atorvastatin
- Fluvastatin
- Lovastatin
- Pitavastatin
- Pravastatin
- Rosuvastatin
- Simvastatin

MYALEPT® (metreleptin) subcutaneous injection (cont.)

American Association of Clinical Endocrinologist Criteria – Clinical Suspicion of Lipodystrophy:

Core clinical characteristic for lipodystrophy	• Loss or absence of subcutaneous body fat in a partial or generalized fashion
Core clinical characteristic for Familial partial lipodystrophy	• Loss of subcutaneous body fat, typically occurring around or shortly after puberty, occurring in the extremities and/or gluteal region with sparing of fat loss or accumulation of excess fat in the face and neck or intra-abdominal area
Supportive clinical characteristics for lipodystrophy	• Presence of diabetes with evidence of severe insulin resistance • Diabetes mellitus with requirement for high doses of insulin, eg, requiring ≥ 200 units/d, or ≥ 2 units/kg/d, or currently taking U-500 insulin • Ketosis-resistant diabetes • Other evidence of severe insulin resistance • Acanthosis nigricans • Polycystic Ovarian Syndrome (PCOS) or PCOS-like symptoms (hyperandrogenism, oligomenorrhea, and/or polycystic ovaries) • Presence of hypertriglyceridemia • Severe hypertriglyceridemia (≥ 500 mg/dL) • Triglyceride levels (≥ 250 mg/dL) that are nonresponsive to therapy and/or modifications to diet • History of pancreatitis associated with hypertriglyceridemia • Evidence of hepatic steatosis or steatohepatitis • Hepatomegaly and/or elevated transaminases in the absence of a known cause of liver disease (eg, viral hepatitis) may be consistent with nonalcoholic fatty liver disease • Radiographic evidence of hepatic steatosis (eg, on ultrasound or computed tomography) • Family history of similar physical appearance and/or history of fat loss • Prominent muscularity and phlebomegaly (enlarged veins) in the extremities • Disproportionate hyperphagia (cannot stop eating, waking up to eat, fighting for food) • Secondary hypogonadism in a male or primary/secondary amenorrhea in a female patient

Resources:

Myalept (metreleptin) product information accessed 12-27-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c986f93b-855d-4ef0-b620-5d41a0513e48

Brown RJ, Araujo-Vilar D, Cheung PT, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. *The Journal of clinical endocrinology and metabolism.* Dec 2016;101(12):4500-4511.

Garg A. Clinical review#: Lipodystrophies: genetic and acquired body fat disorders. *The Journal of clinical endocrinology and metabolism.* Nov 2011;96(11):3313-3325.

MYALEPT® (metreleptin) subcutaneous injection (cont.)

Handelsman Y, Oral EA, Bloomgarden ZT, et al. The clinical approach to the detection of lipodystrophy - an AACE consensus statement. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* Jan-Feb 2013;19(1):107-116.

Pharmaceuticals A. An Overview of the Myalept® Risk Evaluation and Mitigation Strategy (REMS) Program Prescriber Training. 02/04/2017.

UpToDate: Lipodystrophy syndromes. Current through Nov 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/lipodystrophic-syndromes?search=lipodystrophy%20syndromes&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.