Egrifta SV (tesamorelin) MNR
Policy Number: C18465-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DUE BY OR BEFORE
4/28/2021	4/2021	4/26/2022
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
NA	RxPA	Q2 2021 20210428C18465-A

PRODUCTS AFFECTED:
Egrifta SV (tesamorelin)

DRUG CLASS:
Endocrine and Metabolic Agents - Misc

ROUTE OF ADMINISTRATION:
Subcutaneous Injection

PLACE OF SERVICE:
Specialty Pharmacy
The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS:
Egrifta SV SOLR 2MG, Egrifta SOLR 1MG

FDA-APPROVED USES:
Indicated for reduction of excess abdominal fat in HIV-infected adult patients with lipodystrophy
Limitations of Use

- Egrifta (tesamorelin) is not indicated for weight loss and has been shown to have a weight-neutral effect.
- The long-term cardiovascular benefit and safety of Egrifta SV has not been studied.
- There is no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking Egrifta.

COMPENDIAL APPROVED OFF-LABELED USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Lipodystrophy

REQUIRED MEDICAL INFORMATION:
A. LIPODYSTROPHY

1. Documentation of clinically diagnosed human immunodeficiency virus (HIV infection)
   AND

2. Documented diagnosis of HIV-associated lipodystrophy
   AND
3. Member is at risk for medical complications due to excess abdominal fat. Documentation required
   AND
4. Member has excess accumulation of abdominal fat due to HIV-associated lipodystrophy and meets criteria A or B. Documentation of baseline waist circumference required: [ONE: A OR B]
   a. If member is male, both of the following criteria are met: [BOTH]
      i. Waist circumference is greater than 37.4 inches (95 cm)
      ii. Waist-to-hip ratio is greater than 0.94
   b. If member is female, both of the following criteria is met: [BOTH]
      i. Waist circumference is greater than 37 inches (94 cm)
      ii. Waist-to-hip ratio is greater than 0.88

   AND
5. Documentation of body mass index (BMI) of greater than 20kg/m^2
   AND
6. Documentation of fasting Blood Glucose (FBG) is less than 150mg/dL (8.33 mmol/L)
   AND
7. Prescriber attests member does not have an active malignancy, either newly diagnosed or recurrent. Any preexisting malignancy should be inactive, and its treatment complete prior to therapy with Egrifta
   AND
8. If member is a woman of child-bearing age, documentation of a negative pregnancy test
   AND
9. Member is on a stable regimen of highly active antiretroviral therapy for at least 8 weeks [including protease inhibitors, nucleoside reverse transcriptase inhibitor (NRTI), or non-nucleoside reverse transcriptase inhibitors (NNRTI)]
   AND
10. Baseline labs required (*pre-treatment*) and Prescriber agrees to continue monitoring during therapy to submit at time of reauthorization request [ALL]
    NOTE: Pre-treatment and current results will be required for continuation of therapy review
    a) Serum IGF-1 level
       i. Serum IGF-1 levels should be monitored at baseline and during therapy due to the potential increased risk of malignancy from sustained elevation of IGF-1 levels. In the absence of data or guidelines to support drug management in the setting of IGF-1 elevations, it is suggested to monitor IGF-1 at least every 6 months and aim to keep IGF-1 within the normal range of the assay used (Glesby, 2020)
          AND
    b) Serum glucose status
       i. May increase risk of development of diabetes due to glucose intolerance. Monitor periodically for glucose metabolism changes
          AND
    c) For members with diabetes: Retinopathy
       i. Patients with diabetes should be monitored for the development or worsening of retinopathy due to increased IGF-1 levels.

DURATION OF APPROVAL:
Initial authorization: 3 months; Continuation: 6 months
NOTE: Therapy should not be continued beyond 6 months if there is no treatment response, assessed by a decrease in waist circumference. Although safety data do not exist for long term treatment, patients can use this agent for periods of time longer than one year. In accordance with the prescribing information, treatment can be continued if the patient continues to show clinical benefit and has no significant adverse events.

QUANTITY:
2 mg solution for injection: 1 package of 60 vials per 30 days; Dose does not exceed 1.4 mg per day

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, an infectious disease specialist. Submit consultation notes if applicable.
NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually

AGE RESTRICTIONS:
18 to 65 years of age

CONTINUATION OF THERAPY:
A. LIPODYSTROPHY

1. Member currently meets ALL initial coverage criteria AND remains on a stable, compliant antiretroviral regimen [including protease inhibitors, NRTIs, or NNRTIs]. Documentation of current regimen required.
   AND
2. Adherence to therapy at least 85% of the time as confirmed by Prescriber or member's claims history
   NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy
   AND
3. Absence of unacceptable adverse effects or complications from Egrifta (tesamorelin)
   AND
4. Documentation of Positive clinical response* confirmed by an improvement or reduction of visceral adipose tissue (VAT) as documented by waist circumference (WC) or computed tomography (CT) scan. *Treatment response can be defined as: reduction from baseline of VAT by ≥ 10.3% as measured by CT or MRI or a reduction in waist circumference of ≥ 1.4 cm
   NOTE: Treatment should be discontinued if patient has no response at 6 months. Long-term cardiovascular (CV) safety and potential long-term CV benefit of tesamorelin have not been studied; therefore, careful consideration should be given to whether to continue therapy in patients who do not show a response to tesamorelin as measured by a reduction in VAT by waist circumference or CT scan
   AND
5. Documentation of current lab data: Serum IGF-1 level: Discontinue if persistent IGF-1 elevations (e.g., >3 standard deviation scores), Serum glucose status and For members with diabetes: Retinopathy

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Egrifta (tesamorelin) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.
Authorization will not be granted if ANY of the following conditions apply [ANY]: Non-FDA approved indications, Hypersensitivity to tesamorelin or mannitol or any component of the formulation (e.g., pruritus, erythema, flushing, urticaria, rash), Pregnancy

OTHER SPECIAL CONSIDERATIONS:
None

BACKGROUND:

HIV-associated lipodystrophy is a condition characterized by body composition changes, including lipohypertrophy. Patients with lipohypertrophy typically have excess visceral adipose tissue (VAT) in the abdomen but may also accumulate fat in other areas of the body. The underlying mechanisms associated with HIV-associated lipodystrophy may involve changes induced by HIV infection itself and metabolic changes triggered by certain classes of antiretroviral drugs. The mechanisms by which antiretroviral drugs play a role in the development of the lipodystrophy are incompletely understood. HIV-associated lipodystrophy may be attributable to multiple factors including the HIV infection, the antiviral medications used as treatment, and genetic factors.

The prevalence of HIV-associated lipodystrophy has been estimated to range from 10% to 80% among all people living with HIV worldwide (Guzman 2020) with prevalence estimates also varying widely in the United States.

Lipodystrophy can be disfiguring cosmetically and may reduce the quality of life of patients with HIV disease and may pose a barrier to treatment and reduce medical adherence. Clinicians generally recognize that the condition is presented as abnormal body shape changes, including dorsocervical (commonly called "buffalo hump") fat pad enlargement, or buffalo hump; symmetric lipomatosis; breast enlargement; and/or abdominal obesity. Thinning of the face, buttocks, and/or extremities, either alone or in combination with fat accumulation, has also been reported in HIV patients. Other potential indicators of lipodystrophy are metabolic abnormalities, including insulin resistance, glucose intolerance, elevated triglycerides, and elevated cholesterol levels. It is suggested that these abnormalities may be HAART-mediated; however, lipodystrophy may be unrelated to antiretroviral therapy since not all patients who exhibit abnormal fat distribution have been on HAART.

HIV lipodystrophy syndrome may also result in hyperlipidemia, insulin resistance, hyperinsulinemia, and hyperglycemia. Consequently, patients with HIV lipodystrophy syndrome are at increased risk for the development of atherosclerosis and diabetes mellitus. The incidence of diabetes mellitus or atherosclerotic cardiovascular disease is increased secondary to hyperglycemia (from insulin resistance) or hyperlipidemia, respectively. Long-term consequences of this syndrome are not known; however, concern is growing that persistent lipid abnormality may lead to atherosclerotic cardiovascular disease and diabetes.

Objective criteria for diagnosing lipodystrophy are still not established. Therefore, since there is no universally recognized clinical definition and assessment may be difficult in practice as risk factors can be divided into several groups: host factors (gender, age, race, genetic factors, initial total body fat content), environmental factors (nutrition, exercise level) antiretroviral therapy (duration of and drugs used), immunological response, HCV co-infection, as well as HIV-1 infection itself.

There is no gold-standard method for measuring body fat. However, several techniques have been used: anthropometry, bioimpedance analysis, DEXA, computed tomography, magnetic resonance imaging and ultrasonography. However, it is noted that each of these techniques has limitations. Anthropometry and bioimpedance analysis cannot measure regional body fat. Computed tomography and magnetic resonance imaging are costly, therefore use may be limited. Ultrasonography is promising because of its simplicity, safety, availability, and low cost, although it is more operator-dependent than other techniques. DEXA has gained popularity and may be currently the most widely utilized. Few data are available on the comparison of these objective techniques for measuring regional body fat.

Potential interventions for reducing excess VAT include diet and exercise, metformin (especially among patients with diabetes mellitus), tesamorelin, and surgical interventions, including dorso-cervical fat pad liposuction and reduction mammoplasty. (Glesby MJ; UpToDate 2019)

Egrifta (tesamorelin) is the first and only drug approved by the FDA for HIV-associated lipodystrophy. HIV-associated lipodystrophy is defined as physique changes and metabolic abnormalities commonly observed in HIV-infected patients.

Egrifta is a growth hormone-releasing factor (GRF) analog. It is a hypothalamic peptide that acts on pituitary cells in the brain to stimulate the production and release of endogenous growth hormone. GRF stimulates the pituitary to synthesize and secrete growth hormone, which is anabolic and lipolytic. Growth hormone plays an important role in the formation and function of fat cells as well as the overall regulation of fat metabolism. As a synthetic GRF, its effect on visceral adipose tissue (VAT) is believed to be related to the anabolic and catalytic characteristic of growth hormone whose secretion is triggered by GRF; however, the exact mechanism of Egrifta is unclear.

Pivotal Trials

Tesamorelin, a growth hormone–releasing factor analog, was approved by the US Food and Drug Administration (FDA) for treatment of HIV-associated lipodystrophy in November 2010.

FDA approval was based on 2 multicenter, randomized, double-blind, placebo-controlled, Phase 3 that showed that visceral adipose tissue (VAT) was significantly decreased from baseline at 26 weeks and sustained at 52 weeks. (Falutz J) The phase 3 studies included 816 HIV-infected patients LIPO-010 (n = 412), CTR-1011 (n = 404) with excess abdominal fat associated with lipodystrophy.

Both studies consisted of a 26-week Main Phase and a 26-week Extension Phase. The subjects were randomized to receive 2mg Egrifta or placebo subcutaneously daily for 26 weeks. The primary efficacy assessment for each of these studies was the percent change from baseline to Week 26 (Main Phase) in visceral adipose tissue (cm^2), as assessed by computed tomography (CT) scan at L4-L5 vertebral level. In both studies, Egrifta- treated patients completing the 26-week treatment period were re-randomized to blinded therapy with either daily placebo or 2 mg Egrifta for an additional 26-week treatment period (Extension Phase) in order to assess maintenance of VAT reduction and to gather long-term safety data.

Both studies (Study 1 and 2) consisted of a 26-week Main Phase and a 26-week Extension Phase. Main inclusion criteria were:

- Age 18-65 years
- A waist circumference ≥ 95 cm (37.4 inches) and a waist-to-hip ratio ≥ 0.94 for men and ≥ 94 cm (37.0 inches) and ≥ 0.88 for women, respectively, and
- Fasting blood glucose (FBG) <150 mg/dL (8.33 mmol/L)

Main exclusion criteria included BMI ≤ 20 kg/m^2, type 1 diabetes, type 2 diabetes, if previously treated with insulin.

Study One LIPO-010 (n = 412)

This study randomized 412 subjects. At Week 26, treatment with Egrifta resulted in a reduction from baseline in mean trunk fat of 1.0 kg compared with an increase of 0.4 kg in the placebo group. In addition, Egrifta resulted in an increase from baseline in mean lean body mass of 1.3 kg compared with a decrease of 0.2 kg in the placebo group.

Extension Phase

This study re-randomized 207 subjects. Those treated with Egrifta showed no change between Weeks 26 and 52 in mean trunk fat (increase of 0.1 kg vs. increase of 1.4 kg in placebo group) nor was there a change from Week 26 baseline in mean lean body mass (decrease of 0.1 kg vs. decrease of 1.8 kg in placebo group).

LIPO-010 and CTR-1011 comprised a 26-week double-blind (DB) main phase, followed by a 26-week extension phase (the extension phase of CTR-1011 was denoted CTR-1012). In the extension phase, participants who received tesamorelin in the main phase were re-randomized to continue receiving tesamorelin 2 mg/day (T-T group) or switched to placebo (T-P group), whereas all individuals who received placebo in the main phase were assigned to receive tesamorelin (P-T group). The study by Stanley et al. 2014 consisted of a six-month DB treatment phase. The primary efficacy outcome for LIPO-010 and CTR-1011 was the per cent change in VAT at week 26.

Study Two CTR-1011 (n = 404)
This study randomized 404 subjects. At Week 26, treatment with Egrifta resulted in a reduction from baseline in mean trunk fat of 0.8 kg compared with an increase of 0.2 kg in the placebo group. In addition, Egrifta resulted in an increase from baseline in mean lean body mass of 1.2 kg compared with a decrease of 0.03 kg in the placebo group.

Extension Phase
This study re-randomized 177 subjects. Those treated with Egrifta showed no change between Weeks 26 and 52 in mean trunk fat (decrease of 0.5 kg vs. an increase of 1.09 kg in placebo group) nor was there a change from Week 26 baseline in mean lean body mass (increase of 0.1 kg vs. decrease of 1.7 kg in placebo group).

In both studies, there was no adverse effect of Egrifta on lipids or subcutaneous adipose tissue and Egrifta did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load).

Post Hoc Analysis
A post hoc analysis compared tesamorelin non-responders to responders (defined as those with ≥8% reduction in visceral adipose tissue [VAT]) for reduction in triglyceride levels, and glucose homeostasis. The study reported that compared to non-responders, HIV-infected patients receiving tesamorelin with ≥8% reduction in VAT have significantly improved triglyceride levels, adiponectin levels, and preservation of glucose homeostasis.

Summary of Efficacy
- Results from three DB RCTs (LIPO-010, CTR-1011, and Stanley et al. 2014) demonstrated that six months of treatment with tesamorelin was associated with a statistically significantly greater reduction in VAT and waist circumference compared with placebo in HIV-infected patients with abdominal lipohypertrophy.
- The relative reduction in VAT (–12% to –20% across studies) and the absolute reduction in waist circumference (–1.3 to –1.8 cm) associated with tesamorelin treatment versus placebo exceeded the thresholds of 8% and 1 cm, respectively, that was considered to be minimal acceptable decreases that reflect clinical benefit. However, the clinical relevance of the reduction in VAT and waist circumference attributable to tesamorelin is unclear, because tesamorelin treatment was not associated with consistent improvements in body image, which is an important outcome to patients, nor did it improve QoL. Furthermore, the magnitude of reduction in VAT and waist circumference observed in the included studies is unlikely to be seen as clinically relevant by clinicians, while the fact that VAT (as measured by CT scan) is not routinely used to gauge treatment response in clinical practice limits the application of the results to support clinical decision-making.
- A major limitation of the clinical evidence was the limited external validity of the results because the nature of the ART regimens used in the included studies does not reflect treatment regimens used currently in clinical practice in Canada. Specifically, more than half of patients in LIPO-010 and CTR-1011 and approximately 40% of patients in Stanley et al. 2014 were treated with PI-based ARTs that are associated with VAT accumulation, whereas current HIV treatment guidelines recommend ART regimens that mostly comprise INSTIs, which are less likely to cause abdominal lipohypertrophy.
- Treatment with tesamorelin was not associated with any consistent or substantial harm through 52 weeks, although longer-term studies of tesamorelin are needed to adequately assess its long-term safety. There were limited data to evaluate the effects of tesamorelin on important safety outcomes, including the risk of cardiovascular harm, as well as the occurrence of diabetes, cancer, and mortality.

Post-marketing Safety Experience
At the time of approval of Egrifta on November 10, 2010, the FDA requested that the company conduct two large safety clinical trials.

The FDA determined that these two large-scale post-approval clinical trials are no longer required as the current labeling adequately reflects the safety profile of Egrifta. The FDA also concluded that the size of the HIV patient population with lipodystrophy did not make such a requirement feasible.

Professional Societies/Organizations

There are no specific guidelines regarding the treatment of lipodystrophy in patients with HIV.

American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely Initiative

ABIM has not issued recommendations for tesamorelin at this time.

U.S. Department of Health & Human Services, A Working Group of the Office of AIDS Research Advisory Council (ORAC) Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the Use of Antiretroviral Agents in HIV-1 infected adults and adolescents, includes mention of lipodystrophy as a common adverse effect of antiretroviral therapy, but does not include specific treatment recommendations (DHHS, 2018).

HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA): An update of the Infectious Disease Society of America (ISDA) Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus was conducted in 2013. These updated guidelines do not include recommendations for the treatment of lipodystrophy (Aberg, 2013).

APPENDIX:

None

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.

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