Original Effective Date: 04/28/2021
Current Effective Date: 09/06/2023
Last P&T Approval/Version: 07/26/2023
Next Review Due By: 07/2024
Policy Number: C18465-A

Egrifta SV (tesamorelin) MNR

PRODUCTS AFFECTED

Egrifta SV (tesamorelin)

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:
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.

A. LIPODYSTROPHY:
1. Documentation of clinically diagnosed human immunodeficiency virus (HIV infection)
   AND
2. Documentation member has excess accumulation of abdominal fat due to HIV-associated

lipodystrophy and meets criteria A or B. Documentation of baseline waist circumference required. [DOCUMENTATION REQUIRED]:

a. If member is male, both of the following criteria are met:
    i. Waist circumference is greater than 37.4 inches (95 cm)
    ii. Waist-to-hip ratio is greater than 0.94

OR

b. If member is female, both of the following criteria are met:
    i. Waist circumference is greater than 37 inches (94 cm)
    ii. Waist-to-hip ratio is greater than 0.88

AND

3. Documentation of body mass index (BMI) greater than 20kg/m^2
AND
4. Documentation fasting Blood Glucose (FBG) is less than 150mg/dL (8.33 mmol/L)
AND
5. 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 SV (tesamorelin)
AND
6. If member is a woman of child-bearing age, documentation of a negative pregnancy test
AND
7. 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 tesamorelin include: use in member's with disruption of the hypothalamic- pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma, active malignancy, known hypersensitivity to tesamorelin or excipients in EGRIFTA SV, and pregnancy.]
AND
8. 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
9. Documentation of all of the following baseline labs and assessments (*pre-treatment*) and Prescriber agrees to continue monitoring during therapy to submit at time of reauthorization request [DOCUMENTATION REQUIRED]:
NOTE: Pre-treatment and current results will be required for continuation of therapy review
    a. Serum IGF-1 level
    AND
    b. Serum glucose status
    AND
    c. For members with diabetes: Screening for retinopathy

CONTINUATION OF THERAPY:

A. LIPODYSTROPHY:

1. Member remains on a stable, compliant antiretroviral regimen [including protease inhibitors, NRTIs, or NNRTIs]
AND
2. Adherence to therapy at least 85% of the time as confirmed by Prescriber or member's claims history
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
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 member 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 members 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: screening for retinopathy

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, members can use this agent for periods of time longer than one year. In accordance with the prescribing information, treatment can be continued if the member continues to show clinical benefit and has no significant adverse events.

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, an infectious disease or HIV specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests].

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
1.4 mg per day; 1 package per 30 days

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:
Growth Hormone Releasing Hormones (GHRH)

FDA-APPROVED USES:
Indicated for the reduction of excess abdominal fat in HIV-infected adult patients with lipodystrophy
Limitations of Use: *Long-term cardiovascular safety of Egrifta SV (tesamorelin has not been established. Consider risk/benefit of continuation of treatment in patients who have not had a reduction in visceral adipose tissue. Egrifta SV is not indicated for weight loss management as it has a weight neutral effect. There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking Egrifta SV.*

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) “Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization.”
(Subsection 3) “Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or benzodiazepines. (b) Paragraph (a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program.”
Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

State Medicaid
Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) “Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization.”
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Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

Appendix 1
Elevated IGF-1 Levels
EGRIFTA SV stimulates GH production and increases serum IGF-1, a growth factor. The effects of prolonged elevations in IGF-1 levels are unknown. Monitor IGF-1 levels during EGRIFTA SV therapy.

Consider discontinuing EGRIFTA SV in patients with persistent elevations of IGF-1 levels (e.g., >3 SDS), particularly if the efficacy response is not robust.

Glucose Intolerance or Diabetes Mellitus
EGRIFTA SV treatment can result in glucose intolerance. Evaluate glucose status prior to initiating EGRIFTA SV. Monitor all patients treated with EGRIFTA SV periodically to diagnose those who develop impaired glucose tolerance or diabetes. If patients treated with EGRIFTA SV develop glucose intolerance or diabetes, consider discontinuing EGRIFTA SV in patients who do not show a clear efficacy response. EGRIFTA SV increases IGF-1, monitor patients with diabetes who are receiving treatment with EGRIFTA SV at regular intervals for potential development or worsening of retinopathy.

BACKGROUND AND OTHER CONSIDERATIONS

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 (cm2), 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/m2, 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.

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, 2022).

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 updated in 2020. These updated guidelines do not include recommendations for the treatment of lipodystrophy (Thompson, 2020).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Egrifta SV (tesamorelin) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Egrifta SV (tesamorelin) include: use in member's with disruption of the hypothalamic- pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma, active malignancy, known hypersensitivity to tesamorelin or excipients in EGRIFTA SV, and pregnancy.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Egrifta SV SOLR 2MG

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Age Restrictions Quantity Drug Class FDA-Approved Uses Appendix Contraindications/Exclusions/Discontinuation References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Background Contraindications/Exclusions/Discontinuation Available Dosage Form References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file