Facts about *EGRIFTA*™ (tesamorelin for injection)

What is *EGRIFTA*™?

EGRIFTA™ (tesamorelin for injection) is the first and only treatment indicated to reduce excess abdominal fat in HIV-infected patients with lipodystrophy.

There are limitations of use associated with *EGRIFTA*™. Since the long-term cardiovascular safety and potential long-term cardiovascular benefit of *EGRIFTA*™ treatment have not been studied and are not known, careful consideration should be given whether to continue *EGRIFTA*™ treatment in patients who do not show a clear efficacy response as judged by the degree of reduction in visceral adipose tissue (VAT) measured by waist circumference (WC) or CT scan. *EGRIFTA*™ is not indicated for weight loss management (weight neutral effect). There are no data to support improved compliance with antiretroviral therapies in HIV-positive patients taking *EGRIFTA* ™

Clinical research has demonstrated that *EGRIFTA*™ decreases visceral adipose tissue (VAT) and waist circumference (WC) in HIV-infected patients who suffer from excess abdominal fat associated with lipodystrophy.

What is excess abdominal fat in HIV-infected patients with lipodystrophy?

Excess abdominal fat in HIV-infected patients with lipodystrophy is also commonly referred to as abdominal lipohypertrophy, which is characterized by excess deep fat in the abdomen, known as visceral adipose tissue (VAT).

Why Does Excess Abdominal Fat in HIV-infected patients with lipodystrophy occur?

The cause of excess abdominal fat is poorly understood. However, increasing age, gender, genetic factors, severity of HIV disease, and duration and type of antiretroviral therapy have been identified as risk factors.[1]

How Does *EGRIFTA*™ Work?

EGRIFTA™ is a synthetic analogue of growth hormone releasing factor (GRF), shown to reduce visceral fat in HIV-infected patients with excess abdominal fat associated with lipodystrophy. GRF is a hypothalamic peptide that acts on the pituitary cells in the brain to stimulate the synthesis and release of endogenous growth hormone.

What are the Clinical Data of *EGRIFTA*™?

The FDA approval of *EGRIFTA*™ was based on two multi-center, randomized, double-blind, placebo-controlled Phase 3 studies consisting of a 26-week main phase and a 26-week extension phase of 816 HIV-infected patients with excess abdominal fat associated with lipodystrophy.

The primary endpoint of the 26-week main phase was the percent change in VAT from baseline, as assessed by computed tomography (CT) scan at the L4-L5 vertebral level.

In both Phase 3 studies, patients received either *EGRIFTA*™ or placebo for 26 weeks. Patients initially randomized to *EGRIFTA*™ were then re-randomized to receive either *EGRIFTA*™ or placebo for an additional 26-week treatment period, whereas patients receiving placebo were

switched to *EGRIFTA*™ (tesamorelin for injection). In the first study, at baseline, mean VAT was 178 cm^2 for the patients who received *EGRIFTA*™ and was 171 cm^2 for the patients who received placebo. In the second study, at baseline, mean VAT was 186 cm^2 for the patients who received *EGRIFTA*™ and was 195 cm^2 for the patients who received placebo. Patients treated with *EGRIFTA*™ experienced a statistically significant least-squares mean decrease from baseline in VAT of 27 cm^2 compared to an increase of 4 cm^2 for patients on placebo [(95% CI for the mean treatment difference of -31 cm^2 (-39 cm^2, -24 cm^2)] in the first study, and a statistically significant decrease from baseline in VAT of 21 cm^2 compared to no change in VAT for patients on placebo [(95% CI for the mean treatment difference of -21 cm^2 (-29 cm^2, -12 cm^2)] in the second study during the 26-week main phase.

This represents a statistically significant least-squares mean decrease from baseline in VAT of 18% for patients treated with *EGRIFTA*™ compared to an increase of 2% for patients on placebo [(95% CI for the mean treatment difference of -20% (-24%, -15%)] in the first study, and a statistically significant decrease from baseline of 14% for patients treated with *EGRIFTA*™ compared to a decrease of 2% for patients on placebo [(95% CI for the mean treatment difference of -12% (-16%, -7%)] in the second study during the 26-week main phase.

In the first study, at baseline, mean waist circumference was 104 cm for the patients who received *EGRIFTA*™ and was 105 cm for the patients who received placebo. In the second study, at baseline, mean waist circumference was 105 cm for the patients who received *EGRIFTA*™ and for the patients who received placebo. Treatment with *EGRIFTA*™ in a statistically significant least-squares mean decrease from baseline in waist circumference of -3 cm compared to a decrease of -1 cm for patients on placebo [(95% CI for the mean treatment difference of -2 cm (-2.8 cm, -0.9 cm)] in the first study, and a statistically significant decrease from baseline of -2 cm compared to a decrease of -1 cm for patients on placebo [(95% CI for the mean treatment difference of -1 cm (-2.5 cm, -0.3 cm)] in the second study during the 26-week main phase. The decreases in VAT and waist circumference observed after 26 weeks of treatment were sustained in patients who received *EGRIFTA*™ over 52 weeks.

What is the important risk information of *EGRIFTA*™?

EGRIFTA™ is contraindicated in women who are pregnant, in patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma, in patients with known hypersensitivity to tesamorelin and/or mannitol (excipient) and in patients with active malignancies (either newly diagnosed or recurrent). Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with *EGRIFTA* ™. If pregnancy occurs, *EGRIFTA*™ therapy should be discontinued.

EGRIFTA™ induces the release of endogenous growth hormone, a known growth factor, thus patients with active malignancy should not be treated with *EGRIFTA*™. For patients with a history of non-malignant neoplasms, *EGRIFTA*™ therapy should be initiated after careful evaluation of the potential benefit of treatment. For patients with a history of treated and stable malignancies, *EGRIFTA*™ therapy should be initiated only after careful evaluation of the potential benefit of treatment relative to the risk of re-activation of the underlying malignancy. In addition, the decision to start treatment with *EGRIFTA*™ should be considered carefully based on the increased background risk of malignancies in HIV-positive patients.

EGRIFTA™ (tesamorelin for injection) stimulates growth hormone production and increases serum IGF-1. Given that IGF-1 is a growth factor and the effect of prolonged elevations in IGF-1 levels on the development or progression of malignancies is unknown, IGF-1 levels should be monitored closely during *EGRIFTA*™ therapy. Careful consideration should be given to discontinuing *EGRIFTA*™ in patients with persistent elevations of IGF-1 levels (e.g., >3 Standard Deviation Score (SDS)), particularly if the efficacy response is not robust (e.g., based on visceral adipose tissue changes measured by waist circumference or CT scan). During the clinical trials, patients were monitored every three months. Among patients who received *EGRIFTA*™ for 26 weeks, 47.4% had IGF-1 levels greater than 2 SDS, and 35.6% had SDS >3, with this effect seen as early as 13 weeks of treatment. Among those patients who remained on *EGRIFTA*™ (tesamorelin for injection) for a total of 52 weeks, at the end of treatment 33.7% had IGF-1 SDS >2 and 22.6% had IGF-1 SDS >3.

Fluid retention may occur during *EGRIFTA*™ therapy and is thought to be related to the induction of GH secretion. It manifests as increased tissue turgor and musculoskeletal discomfort resulting in a variety of adverse reactions (e.g. edema, arthralgia, carpal tunnel syndrome) which are either transient or resolve with discontinuation of treatment.

EGRIFTA™ (tesamorelin for injection) treatment may result in glucose intolerance. During the Phase 3 clinical trials, the percentages of patients with elevated HbA_{1c} (≥ 6.5%) from baseline to Week 26 were 4.5% and 1.3% in the *EGRIFTA*™ and placebo groups, respectively. An increased risk of developing diabetes with *EGRIFTA*™ (HbA_{1c} level ≥ 6.5%) relative to placebo was observed [intent-to-treat hazard odd ratio of 3.3 (CI 1.4, 9.6)]. Therefore, glucose status should be carefully evaluated prior to initiating *EGRIFTA*™ treatment. In addition, all patients treated with *EGRIFTA*™ should be monitored periodically for changes in glucose metabolism to diagnose those who develop impaired glucose tolerance or diabetes. Diabetes is a known cardiovascular risk factor and patients who develop glucose intolerance have an elevated risk for developing diabetes. Caution should be exercised in treating HIV-positive patients with lipodystrophy with *EGRIFTA*™ if they develop glucose intolerance or diabetes, and careful consideration should be given to discontinuing *EGRIFTA*™ (tesamorelin for injection) treatment in patients who do not show a clear efficacy response as judged by the degree of reduction in visceral adipose tissue by waist circumference or CT scan measurements. Since *EGRIFTA*™ increases IGF-1, patients with diabetes who are receiving ongoing treatment with *EGRIFTA*™ should be monitored at regular intervals for potential development or worsening of retinopathy.

Hypersensitivity reactions may occur in patients treated with *EGRIFTA*™. Hypersensitivity reactions occurred in 3.6% of patients with HIV-associated lipodystrophy treated with *EGRIFTA*™ in the Phase 3 clinical trials. These reactions included pruritus, erythema, flushing, urticaria, and other rash. In cases of suspected hypersensitivity reactions, patients should be advised to seek prompt medical attention and treatment with *EGRIFTA*™ should be discontinued immediately.

EGRIFTA™ treatment may cause injection site reactions including injection site erythema, pruritus, pain, irritation, and bruising. The incidence of injection site reactions was 24.5% in *EGRIFTA*™ treated patients and 14.4% in placebo-treated patients during the first 26 weeks of treatment in the Phase 3 clinical trials. For patients who continued *EGRIFTA*™ for an additional 26 weeks, the incidence of injection site reactions was 6.1%. In order to reduce the incidence of

injection site reactions, it is recommended to rotate the site of injection to different areas of the abdomen.

Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. *EGRIFTA*™ (tesamorelin for injection) has not been studied in patients with acute critical illness. Since *EGRIFTA*™ stimulates growth hormone production, careful consideration should be given to discontinuing *EGRIFTA*™ in critically ill patients.

EGRIFTA™ is contraindicated in pregnant women. During pregnancy, visceral adipose tissue increases due to normal metabolic and hormonal changes. Modifying this physiologic change of pregnancy with *EGRIFTA*™ offers no known benefit and could result in fetal harm. Tesamorelin acetate administration to rats during organogenesis and lactation resulted in hydrocephalus in offspring at a dose approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). If pregnancy occurs, discontinue *EGRIFTA*™ therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Because of both the potential for HIV-1 infection transmission and serious adverse reactions in nursing infants, mothers receiving *EGRIFTA*™ should be instructed not to human milk-feed. It is not known whether *EGRIFTA*™ is excreted in human milk.

Safety and effectiveness in pediatric patients have not been established. *EGRIFTA*™ should not be used in children with open epiphyses, among whom excess GH and IGF-1 may result in linear growth acceleration and excessive growth. There is no information on the use of *EGRIFTA*™ in patients greater than 65 years of age with HIV and lipodystrophy.

Safety, efficacy, and pharmacokinetics of *EGRIFTA*™ in patients with renal or hepatic impairment have not been established.

The most commonly reported adverse reactions (>5% and more frequent than placebo) are arthralgia [13.1% of patients receiving *EGRIFTA*™ and 11.0% of patients receiving placebo], pain in extremity [6.1% of patients receiving *EGRIFTA*™ and 4.6% of patients receiving placebo], myalgia [5.5% of patients receiving *EGRIFTA*™ and 1.9% of patients receiving placebo], injection site erythema [8.5% of patients receiving *EGRIFTA*™ and 2.7% of patients receiving placebo], injection site pruritus [7.6% of patients receiving *EGRIFTA*™ and 0.8% of patients receiving placebo], and peripheral edema [6.1% of patients receiving *EGRIFTA*™ and 2.3% of patients receiving placebo].

During the first 26 weeks of treatment (main phase), discontinuations as a result of adverse reactions occurred in 9.6% of patients receiving *EGRIFTA*™ and 6.8% of patients receiving placebo. Apart from patients with hypersensitivity reactions identified during the studies and who were discontinued per protocol (2.2%), the most common reasons for discontinuation of *EGRIFTA*™ treatment were adverse reactions due to the effect of GH (4.2%) and local injection site reactions (4.6%).

How is *EGRIFTA*™ Administered?
The recommended dose of *EGRIFTA*™ (tesamorelin for injection) is 2 mg injected subcutaneously once a day.[2] The recommended injection site is the abdomen. Injection sites should be rotated to different areas of the abdomen.[3]

Who Developed *EGRIFTA*™?
EGRIFTA™, developed by Theratechnologies, a Canadian biopharmaceutical company, will be marketed in the United States exclusively by EMD Serono.

Please see full prescribing information for *EGRIFTA*™ at www.emdserono.com.

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[1] Lichtenstein KA, Ward DJ, Moorman AC, et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS*. 2001;15: Page 1392, Table 2-3:1393-1394.
[2] Egrifta Label/Prescribing Information. Page 3, Paragraph 3.
[3] Egrifta Label/Prescribing Information. Page 3, Paragraph 7.