HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **EGRIFTA®** safely and effectively. See full prescribing information for **EGRIFTA®.**

EGRIFTA® (tesamorelin for injection), for subcutaneous use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE

EGRIFTA® is a growth hormone releasing factor (GRF) analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. (1)

Limitations of use:

- Long-term cardiovascular benefit and safety of EGRIFTA® have not been studied. (1)
- Not indicated for weight loss management (weight neutral effect). (1)
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA®. (1)

DOSAGE AND ADMINISTRATION

- Recommended dose of EGRIFTA® is 2 mg injected subcutaneously once daily**.** (2.1)
- Reconstitute with diluent provided as recommended. (2.2)
- Administer subcutaneously into abdominal skin, rotating sites. (2.3)

DOSAGE FORMS AND STRENGTHS

- Each vial of EGRIFTA® contains 1 mg of tesamorelin (3). Another vial contains the reconstitution diluent, Sterile Water for Injection, USP**.** (3)

CONTRAINDICATIONS

- Disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism or pituitary tumor/surgery, head irradiation or head trauma (4.1)
- Active malignancy (4.2)
- Known hypersensitivity to tesamorelin and/or mannitol (4.3)
- Pregnancy (4.4)

WARNINGS AND PRECAUTIONS

- Neoplasms: Preexisting malignancy should be inactive and its treatment complete prior to starting EGRIFTA® therapy**.** (5.1)
- Elevated IGF-1: Monitor regularly in all patients. Consider discontinuation in patients with persistent elevations. (5.2)
- Fluid retention: May include edema, arthralgia, and carpal tunnel syndrome. (5.3)
- Glucose intolerance: May develop with EGRIFTA® use. Evaluate glucose status prior to and during therapy with EGRIFTA®. (5.4)
- Hypersensitivity reactions (e.g., rash, urticaria): Advise patients to seek immediate medical attention if suspected. (5.5)
- Injection site reactions: Advise patients to rotate sites. (5.6)
- Acute critical illness: Consider discontinuation**.** (5.7)

ADVERSE REACTIONS

Most commonly reported adverse reactions (>5% and more frequent than placebo): Arthralgia, injection site erythema, injection site pruritus, pain in extremity, peripheral edema, and myalgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact THERA patient support™ **toll free at 1-833-23-THERA (1-833-238-4372) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***

DRUG INTERACTIONS

- Cytochrome P450-metabolized drugs: Monitor carefully if used with EGRIFTA®. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: HIV-1 infected mothers should not human milk-feed to avoid potential postnatal transmission of HIV-1. (8.3)
- Pediatric use: Safety and efficacy not established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EGRIFTA® (tesamorelin for injection) is indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy *[see Clinical Studies (14)]*.

Limitations of Use:

- 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 measured by waist circumference or CT scan.
- EGRIFTA® is not indicated for weight loss management (weight neutral effect).
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA®.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended dose of EGRIFTA® is 2 mg injected subcutaneously once a day.

The recommended injection site is the abdomen. Injection sites should be rotated to different areas of the abdomen. Do not inject into scar tissue, bruises or the navel.

2.2 Reconstitution Procedure

Detailed instructions for reconstituting EGRIFTA® are provided in the INSTRUCTIONS FOR USE leaflet enclosed in the boxes containing EGRIFTA® and diluent.

Two vials of 1 mg of EGRIFTA® must be reconstituted with the diluent provided with the product.

Reconstitute the first 1 mg vial of EGRIFTA® with 2.2 mL of diluent. Mix by rolling the vial gently in your hands for 30 seconds. **Do not shake.** Reconstitute the second 1 mg vial of EGRIFTA® with the entire solution from the first vial. Mix by rolling the vial gently in your hands for 30 seconds. **Do not shake.**

Administer EGRIFTA® immediately following reconstitution and throw away any unused EGRIFTA® solution. If not used immediately, the reconstituted EGRIFTA® solution should be discarded. Do not freeze or refrigerate the reconstituted EGRIFTA® solution.

2.3 Administration

Reconstituted EGRIFTA® solution should always be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. EGRIFTA® must be injected only if the solution is clear, colorless and without particulate matter.

EGRIFTA® should be injected subcutaneously into the skin on the abdomen. Injection sites should be rotated to different areas of the abdomen. Do not inject into scar tissue, bruises or the navel.

3 DOSAGE FORMS AND STRENGTHS

EGRIFTA® (tesamorelin for injection) is supplied in a vial containing 1 mg of tesamorelin as a lyophilized powder. The diluent (Sterile Water for Injection, USP 10 mL) is provided in a separate bottle.

4 CONTRAINDICATIONS

4.1 Disruption of the Hypothalamic-pituitary Axis

EGRIFTA® is contraindicated in patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma.

4.2 Active Malignancy

EGRIFTA® is contraindicated in patients with active malignancy (either newly diagnosed or recurrent). Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with EGRIFTA®.

4.3 Hypersensitivity

EGRIFTA® is contraindicated in patients with known hypersensitivity to tesamorelin and/or mannitol (an excipient) *[see Warnings and Precautions (5.5)]*.

4.4 Pregnancy

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 *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Neoplasms

EGRIFTA® induces the release of endogenous growth hormone (GH), a known growth factor. Thus, patients with active malignancy should not be treated with EGRIFTA® *[see Contraindications (4.2)]*.

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.

5.2 Elevated IGF-1

EGRIFTA® stimulates GH 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 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 standard deviation scores (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® 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.

5.3 Fluid Retention

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.

5.4 Glucose Intolerance

EGRIFTA® treatment may result in glucose intolerance. During the Phase 3 clinical trials, the percentages of patients with elevated HbA_{1c} ($\geq$ 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 $\geq$ 6.5%) relative to placebo was observed [intent-to-treat hazard odds 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® 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.

5.5 Hypersensitivity Reactions

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.

5.6 Injection Site Reactions

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.

5.7 Acute Critical Illness

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® 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.

6 ADVERSE REACTIONS

The most commonly reported adverse reactions are hypersensitivity (e.g., rash, urticaria) reactions due to the effect of GH (e.g., arthralgia, extremity pain, peripheral edema, hyperglycemia, carpal tunnel syndrome), injection site reactions (injection site erythema, pruritus, pain, urticaria, irritation, swelling, hemorrhage).

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%).

During the following 26 weeks of treatment (extension phase), discontinuations as a result of adverse events occurred in 2.4% of patients in the T-T group (patients treated with tesamorelin for Week 0-26 and with tesamorelin for Week 26-52) and 5.2% of patients in the T-P group (patients treated with tesamorelin for Week 0-26 and with placebo for Week 26-52).

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Seven hundred and forty HIV-infected patients with lipodystrophy and excess abdominal fat were exposed to EGRIFTA® in the Phase 3 clinical trials; of these 543 received EGRIFTA® during the initial 26-week placebo-controlled phase *[see Clinical Studies (14)]*.

Adverse reactions that occurred more frequently with EGRIFTA® relative to placebo and had an incidence ≥1% during the first 26 weeks across all studies are presented in Table 1.

Table 1. Adverse Reactions Reported in ≥ 1% and More Frequent in EGRIFTA® –treated than Placebo Patients during the 26-Week Main Phase (Combined Studies)

	Incidence of patients (%) with adverse drug reactions	
System Organ Class Preferred Term	EGRIFTA® (N=543)	Placebo (N=263)
Musculoskeletal and connective tissue disorders		
Arthralgia	13.3	11.0
Pain in extremity	6.1	4.6
Myalgia	5.5	1.9
Musculoskeletal pain	1.8	0.8
Musculoskeletal stiffness	1.7	0.4
Joint stiffness	1.5	0.8
Muscle spasms	1.1	0.8
Joint swelling	1.1	0.0
General disorders and administration site conditions		
Injection site erythema	8.5	2.7
Injection site pruritus	7.6	0.8
Edema peripheral	6.1	2.3
Injection site pain	4.1	3.0
Injection site irritation	2.9	1.1
Pain	1.7	1.1
Injection site hemorrhage	1.7	0.4
Injection site urticaria	1.7	0.4
Injection site swelling	1.5	0.4
Injection site reaction	1.3	0.8
Chest pain	1.1	0.8
Injection site rash	1.1	0.0
Nervous system disorders		
Paresthesia	4.8	2.3
Hypoesthesia	4.2	1.5
Carpal tunnel syndrome	1.5	0.0
Gastrointestinal disorders		

	Incidence of patients (%) with adverse drug reactions	
System Organ Class Preferred Term	EGRIFTA® (N=543)	Placebo (N=263)
Nausea	4.4	3.8
Vomiting	2.6	0.0
Dyspepsia	1.7	0.8
Abdominal pain upper	1.1	0.8
Cardiac disorders		
Palpitations	1.1	0.4
Psychiatric disorders		
Depression	2.0	1.5
Skin and subcutaneous tissue disorders		
Rash	3.7	1.5
Pruritus	2.4	1.1
Night sweats	1.1	0.4
Vascular disorders		
Hypertension	1.3	0.8
Injury, poisoning and procedural complications		
Muscle strain	1.1	0.0
Investigations		
Blood creatine phosphokinase increased	1.5	0.4

Mean levels of fasting blood glucose and fasting insulin were not significantly different between EGRIFTA® -treated and placebo-treated patients after 26 weeks of treatment.

In the EGRIFTA® Phase 3 clinical trials, mean baseline (Week 0) HbA_{1c} was 5.26% among patients in the EGRIFTA® group and 5.28% among those in the placebo group. At Week 26, mean HbA_{1c} was higher among patients treated with EGRIFTA® compared with placebo (5.39% vs. 5.28% for the EGRIFTA® and placebo groups, respectively, mean treatment difference of 0.12%, p=0.0004). Patients receiving EGRIFTA® had an increased risk of developing diabetes (HbA_{1c} level ≥ 6.5%) compared with placebo (4.5% vs. 1.3%), with a hazard ratio of 3.3 (CI 1.4, 9.6).

Adverse reactions observed during Week 26 to 52 of the Phase 3 clinical trials which had an incidence of ≥1% and were seen more frequently with EGRIFTA® relative to placebo are presented in Table 2:

Table 2. Adverse Reactions Reported in ≥ 1% and More Frequent in EGRIFTA®–treated than Placebo Patients during the 26-Week Extension Phase of the Combined Studies (Week 26 to Week 52 of the studies)

	Incidence of patients (%) with adverse drug reactions	
System Organ Class Preferred Term	T-T[1] (Week 26-52) (N=246)	T-P[2](Week 26-52) (N=135)
Musculoskeletal and connective tissue disorders		
Pain in extremity	3.3	0.7
Myalgia	1.2	0.0
General disorders and administration site conditions		
Injection site pruritus	2.0	0.0
Edema peripheral	2.0	0.0
Injection site erythema	1.2	0.0
Nervous system disorders		
Paresthesia	1.6	1.5
Hypoesthesia	1.6	0.7
Neuropathy peripheral	1.6	1.5
Gastrointestinal disorders		
Vomiting	2.0	0.7
Psychiatric disorders		
Depression	1.6	0.7
Insomnia	1.2	0.0
Skin and subcutaneous tissue disorders		
Pruritus	1.2	0.7
Urticaria	1.2	0.0
Night sweats	1.2	0.0
Vascular disorders		
Hypertension	1.6	1.5
Hot flush	1.2	0.7

[1]T-T = tesamorelin for Week 0-26 and tesamorelin for Week 26-52

[2]T-P = tesamorelin for Week 0-26 and placebo for Week 26-52

For patients who continued from Week 26-52, mean levels of fasting blood glucose, fasting insulin, and HbA_{1c} were not different between the T-T and T-P groups.

6.2 Immunogenicity

As with all therapeutic proteins and peptides, there is a potential for in vivo development of anti-EGRIFTA® antibodies. In the combined Phase 3 clinical trials anti-tesamorelin IgG antibodies were detected in 49.5% of patients treated with EGRIFTA® for 26 weeks and 47.4% of patients who received

EGRIFTA® for 52 weeks. In the subset of patients with hypersensitivity reactions, anti-tesamorelin IgG antibodies were detected in 85.2%. Cross-reactivity to endogenous growth hormone-releasing hormone (GHRH) was observed in approximately 60% of patients who developed anti-tesamorelin antibodies. Patients with and without anti-tesamorelin IgG antibodies had similar mean reductions in visceral adipose tissue (VAT) and IGF-1 response suggesting that the presence of antibodies did not alter the efficacy of EGRIFTA®. In a group of patients who had antibodies to tesamorelin after 26 weeks of treatment (56%) and were re-assessed 6 months later, after stopping EGRIFTA® treatment, 18% were still antibody positive.

Neutralizing antibodies to tesamorelin and hGHRH were detected in vitro at Week 52 in 10% and 5% of EGRIFTA®-treated patients, respectively. They did not appear to have an impact on efficacy, as evidenced by comparable changes in VAT and IGF-1 level in patients with or without in vitro neutralizing antibodies.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, methodology, sample handling, timing of sample collection, concomitant medication and underlying disease. For these reasons, comparison of the incidence of antibodies to EGRIFTA® with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Cytochrome P450-Metabolized Drugs

Co-administration of EGRIFTA® with simvastatin, a sensitive CYP3A substrate, showed that EGRIFTA® had no significant impact on the pharmacokinetics profiles of simvastatin in healthy subjects. This result suggests that EGRIFTA® may not significantly affect CYP3A activity. Other isoenzymes of CYP450 have not been evaluated with EGRIFTA®. Published data, however, indicate that GH may modulate cytochrome P450 (CYP450) mediated antipyrine clearance in man. These data suggest that GH may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Because tesamorelin stimulates GH production, careful monitoring is advisable when EGRIFTA® is administered in combination with other drugs known to be metabolized by CYP450 liver enzymes *[see Clinical Pharmacology (12.3)]*.

7.2 11β-Hydroxysteroid Dehydrogenase Type 1 (11βHSD-1)

GH is known to inhibit 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1), a microsomal enzyme required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. Because tesamorelin stimulates GH production, patients receiving glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in maintenance or stress doses following initiation of EGRIFTA®, particularly in patients treated with cortisone acetate and prednisone because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.4)]*.
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 hydrocephaly in offspring at a dose of 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.

Tesamorelin acetate administration to rats during organogenesis and lactation produced hydrocephaly in offspring at a dose of approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). Actual animal dose was 1.2 mg/kg. During organogenesis, lower doses approximately 0.1 to 1 times the clinical dose caused delayed skull ossification in rats. Actual animal doses were 0.1 to 0.6 mg/kg. No adverse developmental effects occurred in rabbits using doses up to approximately 500 times the clinical dose.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States not human milk-feed their infants to avoid risking postnatal transmission of HIV-1 infection**.** 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. Tesamorelin acetate administration to rats during organogenesis and lactation resulted in hydrocephaly in offspring at a dose of approximately two and four times the clinical dose, respectively, based on measured drug exposure (AUC). Actual animal dose was 1.2 mg/kg.

8.4 Pediatric Use

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.

8.5 Geriatric Use

There is no information on the use of EGRIFTA® in patients greater than 65 years of age with HIV and lipodystrophy.

8.6 Renal and Hepatic Impairment

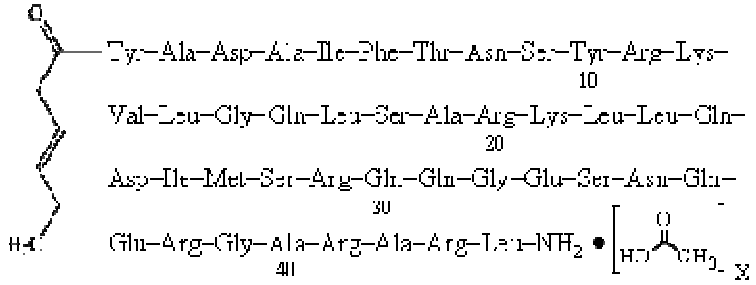
Safety, efficacy, and pharmacokinetics of EGRIFTA® in patients with renal or hepatic impairment have not been established.

10 OVERDOSAGE

No data are available on overdosage.

11 DESCRIPTION

EGRIFTA® contains tesamorelin (as the acetate salt), an analog of human growth hormone-releasing factor (GRF). The peptide precursor of tesamorelin acetate is produced synthetically and is comprised of the 44 amino acid sequence of human GRF. Tesamorelin acetate is made by attaching a hexenoyl moiety, a C6 chain with a double bond at position 3, to the tyrosine residue at the N-terminal part of the molecule. The molecular formula of tesamorelin acetate is $C_{221}H_{366}N_{72}O_{67}S \bullet x\ C_2H_4O_2$ ($x \approx 7$) and its molecular weight (free base) is 5135.9 Daltons. The structural formula of tesamorelin acetate is:



EGRIFTA® is a sterile, white to off-white, preservative-free lyophilized powder for subcutaneous injection. After reconstitution with the supplied diluent (Sterile Water for Injection, USP), a solution of EGRIFTA® is clear and colorless. Each single-use vial of EGRIFTA® contains 1 mg of tesamorelin as the free base (1.1 mg tesamorelin acetate, anhydrous) and the following inactive ingredient: 50 mg mannitol, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In vitro, tesamorelin binds and stimulates human GRF receptors with similar potency as the endogenous GRF *[see Clinical Pharmacology (12.2)]*.

Growth Hormone-Releasing Factor (GRF), also known as growth hormone-releasing hormone (GHRH), is a hypothalamic peptide that acts on the pituitary somatotroph cells to stimulate the synthesis and pulsatile release of endogenous growth hormone (GH), which is both anabolic and lipolytic. GH exerts its effects by interacting with specific receptors on a variety of target cells, including chondrocytes, osteoblasts, myocytes, hepatocytes, and adipocytes, resulting in a host of pharmacodynamic effects. Some, but not all these effects, are primarily mediated by IGF-1 produced in the liver and in peripheral tissues.

12.2 Pharmacodynamics

Effects on IGF-1 and IGFBP-3 levels

Tesamorelin stimulates growth hormone secretion, and subsequently increases IGF-1 and IGFBP-3 levels *[see Clinical Studies (14)]*.

Other Pituitary Hormones

No clinically significant changes in the levels of other pituitary hormones, including thyroid-stimulating hormone (TSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH) and prolactin, were observed in subjects receiving EGRIFTA® in Phase 3 clinical trials.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of EGRIFTA® after subcutaneous administration of a 2 mg dose was determined to be less than 4% in healthy adult subjects. Single and multiple dose pharmacokinetics of EGRIFTA® have been characterized in healthy subjects and HIV-infected patients without lipodystrophy following 2 mg subcutaneous administration.

The mean values [coefficient of variation (CV)] of the extent of absorption (AUC) for tesamorelin were 634.6 (72.4) and 852.8 (91.9) pg**.**h/mL in healthy subjects and HIV-infected patients, respectively, after a single subcutaneous administration of a 2 mg EGRIFTA® dose. The mean (CV) peak tesamorelin concentration (C_{max}) values were 2874.6 (43.9) pg/mL in healthy subjects and 2822.3 (48.9) pg/mL in HIV-infected patients. The median peak plasma tesamorelin concentration (T_{max}) was 0.15 h in both populations.

Distribution

The mean volume of distribution (±SD) of tesamorelin following a single subcutaneous administration was 9.4±3.1 L/kg in healthy subjects and 10.5±6.1 L/kg in HIV-infected patients.

Metabolism

No formal metabolism studies have been performed in humans.

Elimination

Mean elimination half-life ($T_{1/2}$) of tesamorelin was 26 and 38 minutes in healthy subjects and HIV-infected patients, respectively, after subcutaneous administration for 14 consecutive days.

Drug Interactions

Simvastatin

The effect of multiple dose administration of EGRIFTA® (2 mg) on the pharmacokinetics of simvastatin and simvastatin acid was evaluated in healthy subjects. Co-administration of EGRIFTA® and simvastatin (a sensitive CYP3A substrate) resulted in 8% decrease in extent of absorption (AUC_{inf}) and 5% increase in rate of absorption (C_{max}) of simvastatin. For simvastatin acid there was a 15% decrease in AUC_{inf} and 1% decrease in C_{max} *[see Drug Interactions (7.1)]*.

Ritonavir

The effect of multiple dose administration of EGRIFTA® (2 mg) on the pharmacokinetics of ritonavir was evaluated in healthy subjects. Co-administration of EGRIFTA® with ritonavir resulted in 9% decrease in AUC_{inf} and 11% decrease in C_{max} of ritonavir *[see Drug Interactions]*.

Specific Populations

Pharmacokinetics of tesamorelin in patients with renal or hepatic impairment, in pediatric patients, or in elderly patients has not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Life-time carcinogenicity studies in rodents have not been conducted with tesamorelin acetate. No potential mutagenicity of tesamorelin acetate was revealed in a battery of tests including induction of gene mutations in bacteria (the Ames test), gene mutations in mammalian cells grown in vitro (hamster CHOK1 cells), and chromosomal damage in intact animals (bone marrow cells in mice). There was no effect on fertility in male or female rats following administration of tesamorelin acetate at doses up to 0.6 mg/kg (approximately equal to clinical exposure) for 28 days in males or 14 days in females. In the 26-week toxicity study in rats, females given approximately 16 and 25 times the clinical dose were more likely to be in diestrus.

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in HIV-infected patients with lipodystrophy and excess abdominal fat (abdominal lipohypertrophy). 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 or with oral hypoglycemic or insulin-sensitizing agents, history of malignancy, and hypopituitarism. Patients were on a stable anti-retroviral regimen for at least 8 weeks prior to randomization. Patients meeting the inclusion/exclusion criteria were randomized in a 2:1 ratio to receive 2 mg 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 (VAT), as assessed by computed tomography (CT) scan at L4-L5 vertebral level. Secondary endpoints included changes from baseline in patient-reported outcomes related to body image, triglycerides, ratio of total cholesterol to HDL cholesterol, IGF-1 levels, and safety parameters. Other endpoints included changes from baseline in waist circumference, abdominal subcutaneous tissue (SAT), trunk fat, and lean body mass. 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. For inclusion in the Extension Phase studies, subjects must have completed the Main Phase with FBG ≤ 150 mg/dL.

Main Phase (Baseline to Week 26):

Study 1

This study randomized 412 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either EGRIFTA® (N=273) or placebo (N=137). At baseline for the two groups combined, mean age was 48 years; 86% were male; 75% were white, 14% were Black/African American, and 8% were Hispanic; mean weight was 90 kg; mean BMI was 29 kg/m^2; mean waist circumference was 104 cm; mean hip circumference was 100 cm; mean VAT was 176 cm^2; mean CD4 cell count was 606 $cells/mm^3$; 69% had undetectable viral load (<50 copies/mL); and 33.7% randomized to EGRIFTA® and 36.6% randomized to placebo had impaired glucose tolerance, while 5.6% randomized to EGRIFTA® and 6.7% randomized to placebo had diet-controlled diabetes mellitus. The twenty-six week completion rate in Study 1 was 80%.

Study 2

This study randomized 404 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either EGRIFTA® (N=270) or placebo (N=126). At baseline for the two groups combined, mean age was 48 years; 84% were male; 77% were white, 12% were Black/African American, and 9% were Hispanic; mean weight was 88 kg; mean BMI was 29 kg/m^2; mean waist circumference was 105 cm; mean hip circumference was 100 cm; mean VAT was 189 cm^2; mean CD4 cell count was 592 $cells/mm^3$; 83% had undetectable viral load (<50 copies/mL); and 44.1% randomized to EGRIFTA® and 39.7% randomized to placebo had impaired glucose tolerance, while 9.3% randomized to EGRIFTA® and 9.5% randomized to placebo had diet-controlled diabetes mellitus. The twenty-six week completion rate in Study 2 was 74%.

Results for the Main Phases of Studies 1 and 2 are presented in Tables 3 and 4.

Table 3: Changes from Baseline to Week 26 in Visceral Adipose Tissue (cm^2) by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

MAIN PHASE (Baseline-Week 26)				
	Study 1		Study 2	
	EGRIFTA® (N=273)	Placebo (N=137)	EGRIFTA® (N=270)	Placebo (N=126)
Baseline (cm^2)	178 (77)	171 (77)	186 (87)	195 (95)
Change (cm^2)	-27	4	-21	-0
Mean treatment difference (95% CI)	-31 (-39,-24)		-21 (-29,-12)	
Mean change (%)[1]	-18	2	-14	-2
Mean treatment difference (95% CI)[1]	-20 (-24, -15)		-12 (-16, -7)	

Baseline data are expressed as mean (SD); Change refers to least-squares mean (LSM); CI: confidence interval.

[1] Results derived from the statistical model: Ln(VAT Week 26/VAT Baseline) = Ln(VAT Baseline) + treatment group

Table 4: Changes from Baseline to Week 26 in IGF-1, IGFBP-3, Weight, and Waist Circumference by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

MAIN PHASE (Baseline-Week 26)					
		Study 1		Study 2	
		EGRIFTA® (N=273)	Placebo (N=137)	EGRIFTA® (N=270)	Placebo (N=126)
IGF-1 (ng/mL)	Baseline	161 (59)	168 (75)	146 (66)	149 (59)
	Change	107	-15	108	3
	Mean treatment difference (95% CI)	122 (101, 141)		105 (85, 126)	
IGFBP-3 (mg/L)	Baseline	3 (1)	3 (1)	3 (1)	3 (1)
	Change	0.4	-0.2	0.8	-0.0
	Mean treatment difference (95% CI)	0.6 (0.5, 0.8)		0.8 (0.5, 1.0)	
Weight (kg)	Baseline	90 (14)	90 (14)	89 (14)	87 (16)
	Change	-0.4	0.0	0.5	0.3
	Mean treatment difference (95% CI)	-0.4 (-1.3, 0.5)		0.2 (-0.7, 1.3)	
Waist circumference (cm)	Baseline	104 (10)	105 (9)	105 (9)	105 (9)
	Change	-3 (5)	-1 (4)	-2 (5)	-1 (5)
	Mean treatment difference (95% CI)	-2 (-2.8, -0.9)		-1 (-2.5, -0.3)	

Baseline data are expressed as mean (SD); Change refers to least-squares mean (LSM); CI: confidence interval.

A subgroup analysis by gender showed that there were no statistical differences in the percent change from baseline in visceral adipose tissue (VAT) and IGF-1 responses, respectively, between males and females.

At Week 26, treatment with EGRIFTA® resulted in a reduction from baseline in mean trunk fat of 1.0 kg in Study 1 and 0.8 kg in Study 2, respectively (compared with an increase of 0.4 kg in Study 1 and of 0.2 kg in Study 2, respectively, in patients receiving placebo). Treatment with EGRIFTA® resulted in an increase from baseline in mean lean body mass of 1.3 kg in Study 1 and of 1.2 kg in Study 2, respectively (compared with a decrease of 0.2 kg in Study 1 and of 0.03 kg in Study 2, respectively, in patients receiving placebo).

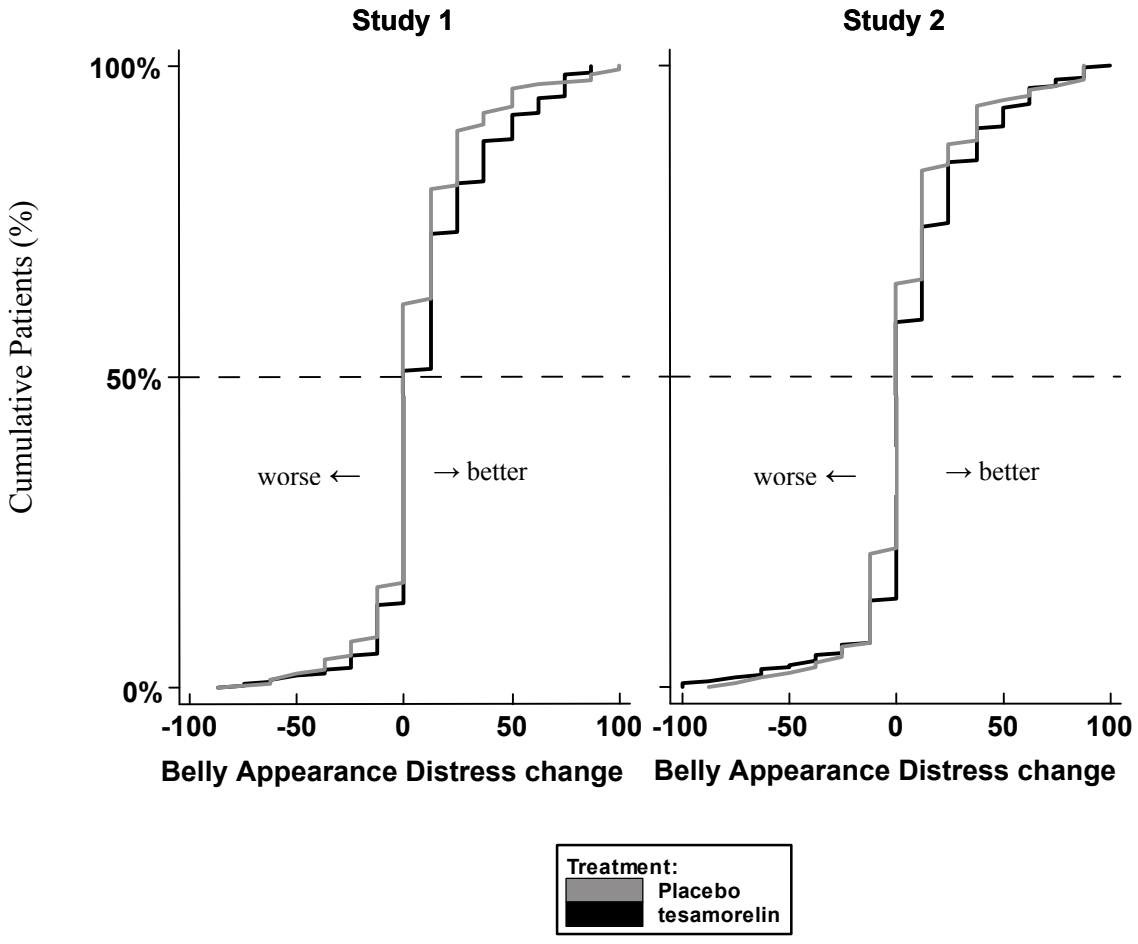
On average, there were no adverse effects of EGRIFTA® on lipids or subcutaneous adipose tissue (SAT). EGRIFTA® did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load).

Patient Reported Outcomes

Patients rated the degree of distress associated with their belly appearance on a 9 -point rating scale that was then transformed to a score from 0 (extremely upsetting and distressing) to 100 (extremely encouraging). A score of 50 indicated neutral (no feeling either way). A positive change from baseline score indicated improvement, i.e., less distress.

The cumulative distribution of response (change from baseline to 26 weeks) is shown in Figure 1 for both treatment groups. A curve shifted to the right on this scale indicates a greater percentage of patients reporting improvement.

Figure 1. Cumulative Distribution of Response for Belly Appearance Distress



Extension Phase (Weeks 26-52):

In the double-blind Extension Phase, patients on EGRIFTA® completing the 26-week Main Phase were re-randomized to receive 2 mg EGRIFTA® or placebo.

Study 1

This study re-randomized 207 HIV-infected patients with lipodystrophy who completed EGRIFTA® treatment in the Main Phase to receive either EGRIFTA® (N=154) or placebo (N=50) for an additional 26-week duration (3:1 randomization ratio). At baseline (Week 26) for the two groups combined, mean age was 48 years; 88% were male; 78% were white, 12% were Black/African American, and 8% were Hispanic; mean weight was 90 kg; mean BMI was 29 kg/m^2; mean waist circumference was 102 cm; mean hip circumference was 100 cm; mean VAT was 145 cm^2; mean CD4 cell count was 639 cells/mm^3; 68% had undetectable viral load (<50 copies/mL); and for those EGRIFTA®-treated patients completing the 26-week treatment period that were re-randomized to EGRIFTA® (T-T group) or re-randomized to placebo, 36.6% and 32.0%, respectively, had impaired glucose tolerance, while 2.0% re-randomized to EGRIFTA® and 6.0% re-randomized to placebo had diet-controlled diabetes mellitus. The completion rate for patients randomized into the extension phase of Study 1 was 83%.

Study 2

This study re-randomized 177 HIV-infected patients with lipodystrophy who completed EGRIFTA® treatment in the Main Phase to receive either EGRIFTA® (N=92) or placebo (N=85) for an additional 26-week duration (1:1 randomization ratio). At baseline (Week 26) for the two groups combined, mean age was 48 years; 90% were male; 84% were white, 9% were Black/African American, and 7% were Hispanic; mean weight was 89 kg; mean BMI was 28 kg/m^2; mean waist circumference was 105 cm; mean hip circumference was 100 cm; mean VAT was 172 cm^2; mean CD4 cell count was 579 cells/mm^3; 82% had undetectable viral load (<50 copies/mL); and for those EGRIFTA®-treated patients completing the 26-week treatment period that were re-randomized to EGRIFTA® (T-T group) or re-randomized to placebo, 48.9% and 50.6%, respectively, had impaired glucose tolerance, while 4.3% re-randomized to EGRIFTA® and 12.9% re-randomized to placebo had diet-controlled diabetes mellitus. The completion rate for patients randomized into the extension phase of Study 2 was 81%.

Results for the Extension Phases of Studies 1 and 2 are presented in Tables 5 and 6.

Table 5: Changes from Week 26 Baseline to Week 52 in Visceral Adipose Tissue (cm^2) by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

EXTENSION PHASE (Week 26-52)				
	Study 1		Study 2	
	T-T[1] (Week 26-52) (N=154)	T-P[2] (Week 26-52) (N=50)	T-T[1] (Week 26-52) (N=92)	T-P[2] (Week 26-52) (N=85)
Week 26 (cm^2)	145 (72)	144 (72)	166 (89)	177 (88)
Change (cm^2)	3	25	-11	24
Mean treatment difference (95% CI)	-22 (-34, -10)		-35 (-48, -22)	
Mean change (%)[3]	0	22	-5	16
Mean treatment difference (95% CI)[3]	-17 (-24, -10)		-18 (-24, -11)	

Week 26 baseline data are expressed as mean (SD). Change refers to least-squares mean (LSM); CI: confidence interval.

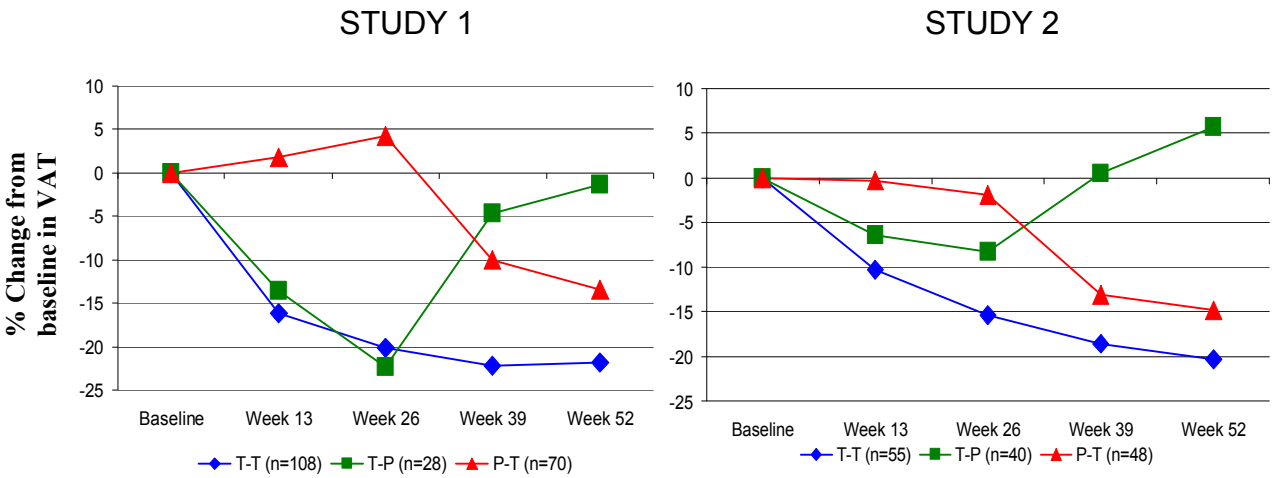
[1]T-T = tesamorelin for Weeks 0-26 and tesamorelin for Weeks 26-52

[2]T-P = tesamorelin for Weeks 0-26 and placebo for Weeks 26-52

[3]Results derived from the statistical model: Ln(VAT Week 52/Week 26) = Ln(Week 26 VAT) + treatment group

Figure 2. shows the percent change in VAT from baseline (Week 0) over time until 52 weeks in completer patients.

Figure 2. Percent Change from Baseline in VAT over Time



Data in Figure 2 are expressed as mean values. T-T (tesamorelin to tesamorelin) refers to the group of patients who received tesamorelin for Weeks 0-26 and were re-randomized to tesamorelin for Weeks 26-52. T-P (tesamorelin to placebo) refers to the group of patients who received tesamorelin for Weeks 0 -26 and were re-randomized to placebo for Weeks 26-52. P-T (placebo to tesamorelin) refers to the group of patients who received placebo for Weeks 0 -26 and were switched to tesamorelin (treated open label) for Weeks 26-52.

Table 6: Changes from Week 26 Baseline to Week 52 in IGF-1, IGFBP-3, Weight, and Waist Circumference by Treatment Group (Intent-To-Treat Population with Last Observation Carried Forward)

EXTENSION PHASE (Weeks 26-52)					
		Study 1		**Study 2**	
		T-T[1] (Week 26-52) (N=154)	T-P[2] (Week 26-52) (N=50)	T-T[1] (Week 26-52) (N=92)	T-P[2] (Week 26-52) (N=85)
IGF-1 (ng/mL)	Week 26	291 (124)	281 (105)	280 (134)	269 (110)
	Change	-59	-137	-25	-135
	Mean treatment difference (95% CI)	78 (50, 106)		110 (87, 134)	
IGFBP-3 (mg/L)	Week 26	3 (1)	3 (1)	3 (1)	3 (1)
	Change	-0.2	-0.5	-0.3	-0.9
	Mean treatment difference (95% CI)	0.3 (-0.0, 0.6)		0.6 (0.3, 0.9)	
Weight (kg)	Week 26	89 (14)	92 (17)	89 (13)	90 (14)
	Change	0.2	0.6	-0.5	0.1
	Mean treatment difference (95% CI)	-0.4 (-2, 1)		-0.6 (-2, 1)	
Waist circumference (cm)	Week 26	101 (10)	102 (12)	101 (9)	103 (11)
	Change	-0.2	2.4	-1.1	0.2
	Mean treatment difference (95% CI)	-2.6 (-4, -1)		-1.3 (-2, 0)	

Week 26 baseline data are expressed as mean (SD); Change refers to least -squares mean (LSM); CI: confidence interval.

[1]T-T = tesamorelin for Week 0-26 and tesamorelin for Week 26-52

[2]T-P = tesamorelin for Week 0-26 and placebo for Week 26-52

Patients treated with EGRIFTA® for 52 weeks (T-T group) showed no change between Weeks 26 and 52 in mean trunk fat (increase of 0.1 kg in Study 1 and decrease of 0.5 kg in Study 2, respectively, compared with an increase of 1.4 kg in patients in the T-P group in Study 1 and an increase of 1.09 kg in Study 2, respectively) nor was there a change from Week 26 baseline in mean lean body mass (decrease of 0.1 kg in Study 1 and increase of 0.1 kg in Study 2, respectively, compared with a decrease of 1.8 kg in patients in the T-P group in Study 1 and a decrease of 1.7 kg in Study 2, respectively).

There was no adverse effect of EGRIFTA® on lipids or subcutaneous adipose tissue (SAT). EGRIFTA® did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load).

16 HOW SUPPLIED/STORAGE AND HANDLING

EGRIFTA® (tesamorelin for injection) is supplied as a sterile, white to off-white lyophilized powder. Each single-use vial of EGRIFTA® contains 1 mg of tesamorelin as the free base (1.1 mg tesamorelin acetate, anhydrous) and the following inactive ingredient: 50 mg mannitol, USP.

EGRIFTA® is available in a package comprised of two boxes. One box contains 60 vials of 1 mg each of EGRIFTA® and a second box contains 30 single-use 10 mL bottles of reconstitution diluent (Sterile Water for Injection, USP), disposable syringes, and needles sufficient for a 30 day supply.

After reconstitution with Sterile Water for Injection, USP the reconstituted solution concentration is 1 mg/mL and should be injected immediately.

EGRIFTA® vials should be protected from light and be kept in the original box until time of use. Non-reconstituted EGRIFTA® must be stored at refrigerated temperature, between 2°C to 8°C (36°F to 46°F). The reconstitution diluent (Sterile Water for Injection, USP), syringes and needles should be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F).

Syringes and needles are for single-use by a single patient and should never be shared between patients.

NDC 62064-011-60

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Patient Instructions for Use).

- Fluid retention (5.3) – Advise patients that treatment with EGRIFTA® may cause symptoms consistent with fluid retention, including edema, arthralgia, and carpal tunnel syndrome. These reactions are either transient or resolve with discontinuation of treatment.
- Hypersensitivity Reactions (5.5) – Advise patients that hypersensitivity reactions (e.g., rash, urticaria) may occur during treatment with EGRIFTA®. Advise patients to seek prompt medical attention and to immediately discontinue treatment with EGRIFTA®.
- Injection Site Reactions (5.6) – Advise patients of possible injection site reactions, including injection site erythema, pruritus, pain, irritation, and bruising. To reduce the incidence of injection site reactions, advise patients to rotate the site of injection.
- Counsel patients that they should never share an EGRIFTA® syringe with another person, even if the needle is changed. Sharing of syringes or needles between patients may pose a risk of transmission of infection.

Pregnancy

Advise women to discontinue EGRIFTA® if pregnancy occurs, as the drug offers no known benefit to pregnant women and could result in fetal harm *[see Contraindications (4.4) and Use in Specific Populations (8.1)]*.

Nursing Mothers

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 *[see Use in Specific Populations (8.3)]*.

Distributed by: Theratechnologies Inc., Montreal, Québec, Canada H3A 1T8

Revised: 07/2018