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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

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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.

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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)]*.

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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} (≥ 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 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

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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).

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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		

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	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:

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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

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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

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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.

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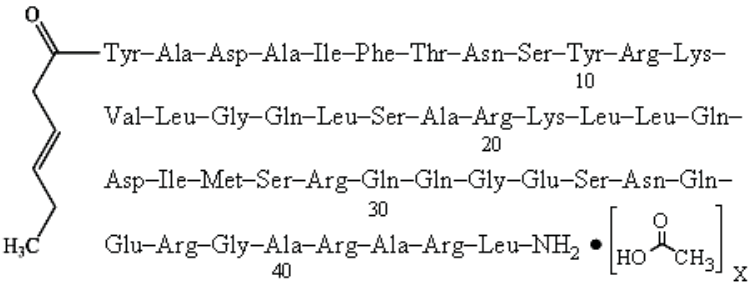
10 OVERDOSAGE

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.

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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.

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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

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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.

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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.

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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).

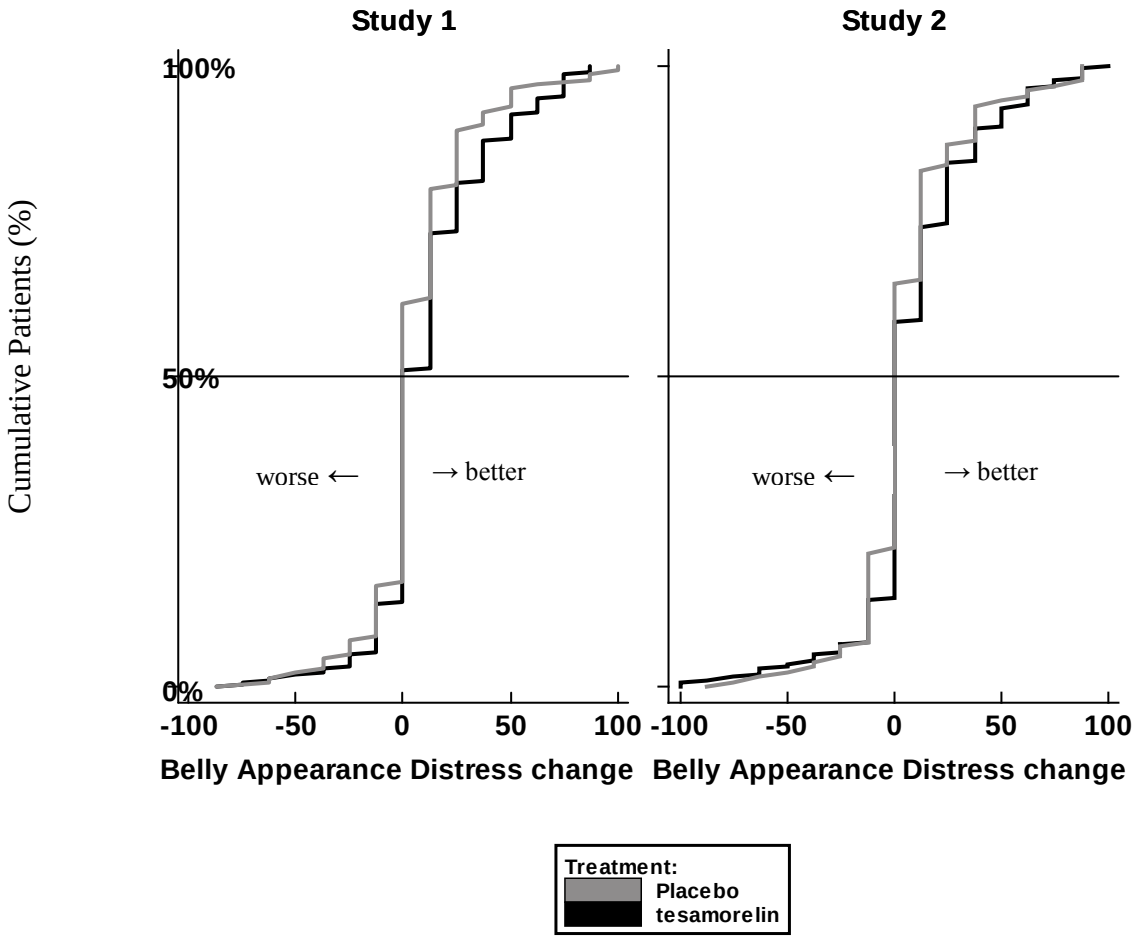
On average, there were no adverse effects of EGRIFTA® on lipids or subcutaneous adipose tissue (SAT). EGRIFTA® did not adversely alter antiretroviral effectiveness, such as mean circulating levels of CD4 counts or HIV-1 RNA (viral load).

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



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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.

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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.

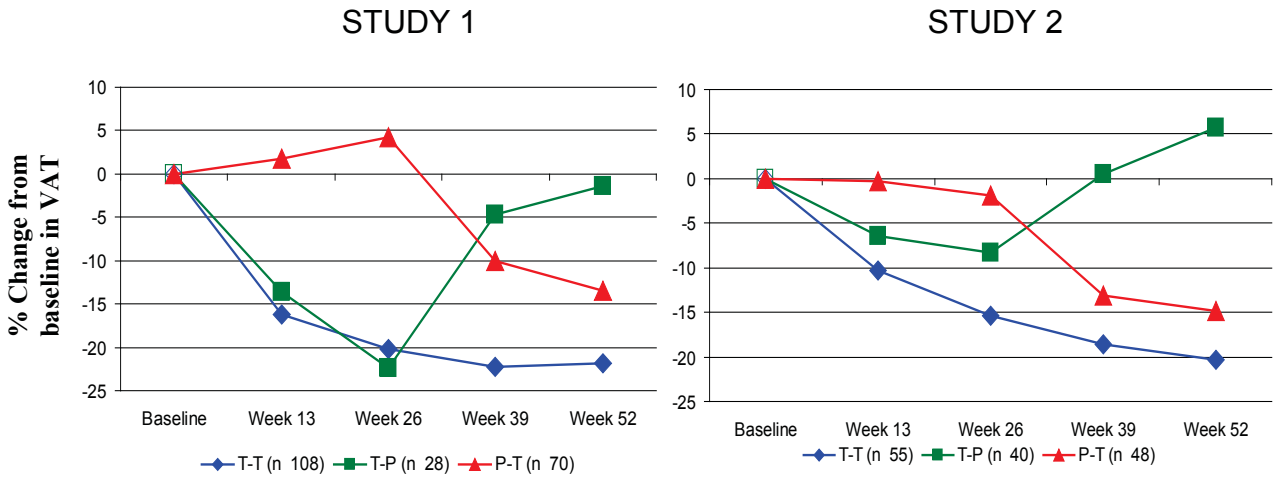
[1]T-T = tesamorelin for Weeks 0-26 and tesamorelin for Weeks 26-52

[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



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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).

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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.

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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)]*.

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

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Patient Information

EGRIFTA® (eh-GRIF-tuh)
(tesamorelin for injection)
for subcutaneous use

Read the Patient Information that comes with EGRIFTA® before you start to take it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is EGRIFTA®?

- EGRIFTA® is an injectable prescription medicine to reduce the excess in abdominal fat in HIV-infected patients with lipodystrophy. EGRIFTA® contains a growth hormone-releasing factor (GRF).
- The impact and safety of EGRIFTA® on cardiovascular health has not been studied.
- EGRIFTA® is not indicated for weight loss management.
- It is not known whether taking EGRIFTA® helps improve compliance with anti-retroviral medications.
- It is not known if EGRIFTA® is safe and effective in children. EGRIFTA® is not recommended to be used in children.

Who should not use EGRIFTA®?

Do not use EGRIFTA® if you:

- have pituitary gland tumor, pituitary gland surgery or other problems related to your pituitary gland.
- have active cancer (either newly diagnosed or recurrent) or are receiving treatment for cancer.
- are allergic to tesamorelin or any of the ingredients in EGRIFTA®. See the end of this leaflet for a complete list of ingredients in EGRIFTA®
- are pregnant or become pregnant. If you become pregnant, stop using EGRIFTA® and talk with your healthcare provider. See "What should I tell my healthcare provider before using EGRIFTA®?"

What should I tell my healthcare provider before using EGRIFTA®?

Before using EGRIFTA®, tell your healthcare provider if you:

- have or have had cancer
- have diabetes
- are breastfeeding or plan to breastfeed. It is not known if EGRIFTA® passes into your breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers not breastfeed to avoid the risk of passing HIV infection to your baby. Talk with your

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healthcare provider about the best way to feed your baby if you are taking EGRIFTA®

- have kidney or liver problems
- have any other medical condition.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. EGRIFTA® may affect the way other medicines work, and other medicines may affect how EGRIFTA® works.

Know the medicines you take. Keep a list with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I use EGRIFTA®?

- **Read the detailed "Instructions for Use"** that comes with EGRIFTA® before you start using EGRIFTA®. Your healthcare provider will show you how to inject EGRIFTA®.
- Use EGRIFTA® exactly as prescribed by your healthcare provider.
- Inject EGRIFTA® under the skin (subcutaneously) of your stomach area (abdomen).
- Change (rotate) the injection site on your stomach area (abdomen) with each dose. Do not inject EGRIFTA® into scar tissue, bruises or your navel.
- **Do not** share needles or syringes with other people. Sharing of needles can result in the transmission of infectious diseases, such as HIV.

What are the possible side effects of EGRIFTA®?

EGRIFTA® may cause serious side effects including:

- **Serious allergic reaction.** Some people taking EGRIFTA® may have an allergic reaction.

  Stop using EGRIFTA® and get emergency help right away if you have any of the following symptoms:

  - a rash over your body
  - hives
  - swelling of your face or throat
  - shortness of breath or trouble breathing
  - fast heartbeat
  - feeling of faintness or fainting
- **Swelling (fluid retention).** EGRIFTA® can cause swelling in some parts of your body. Call your healthcare provider if you have an increase in joint pain, or pain or numbness in your hands or wrist (carpal tunnel syndrome).

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- **Increase in glucose (blood sugar) intolerance and diabetes.** Your healthcare provider will measure your blood sugar periodically.
- **Injection site reactions.** Change (rotate) your injection site to help lower your risk for injection site reactions. Call your healthcare provider for medical advice if you have the following symptoms around the area of the injection site:
    - redness
    - itching
    - pain
    - irritation
    - bleeding
    - rash
    - swelling

The most common side effects of EGRIFTA® include:

- joint pain
- pain in legs and arms
- swelling in your legs
- muscle soreness
- tingling, numbness and pricking
- nausea
- vomiting
- rash
- itching

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of EGRIFTA®. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088

You may also report side effects to THERA patient support™ toll-free at 1-833-23-THERA (1-833-238-4372).

How do I store EGRIFTA®?

- EGRIFTA® has two boxes dispensed by the pharmacy:
    - Store the Medication Box of EGRIFTA® vials in the refrigerator between 2°C to 8°C (36°F to 46°F).

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  - Store the box of Sterile Water for Injection, syringes and needles at room temperature between 20°C to 25°C (68°F to 77°F).

- Keep EGRIFTA® vials in Medication Box away from light.
- Do not freeze.
- Do not use EGRIFTA® after the expiration date printed on the carton and vial labels.
- After mixing, use EGRIFTA® right away and throw away any unused EGRIFTA®. Do not store mixed EGRIFTA®. Also, throw away the used bottle of Sterile Water for Injection.

Keep EGRIFTA® and all medicines out of the reach of children.

General information about the safe and effective use of EGRIFTA®

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EGRIFTA® for a condition for which it was not prescribed. Do not give EGRIFTA® to other people, even if they have the same symptoms you have. It may harm them.

Do not share your EGRIFTA® syringe or needles with another person. You may give an infection to them or get an infection from them.

This Patient Information leaflet summarizes the most important information about EGRIFTA®. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about EGRIFTA® that is written for healthcare professionals.

For more information about EGRIFTA®, go to www.EGRIFTA.com or contact THERA patient support™ toll-free at 1-833-23-THERA (1-833-238-4372).

What are the ingredients in EGRIFTA®?

Active ingredient: tesamorelin
Inactive ingredients: mannitol and Sterile Water for Injection

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by: Jubilant HollisterStier General Partnership, 16751 Trans-Canada Highway, Montreal, Québec, Canada H9H 4J4

Revised: 07/2018

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Instructions for Use

EGRIFTA® (eh-GRIF-tuh)
(tesamorelin for injection)
for subcutaneous use

Be sure that you read, understand, and follow this "Instructions for Use" before using EGRIFTA®. Your healthcare provider should show you how to mix and inject EGRIFTA® before you inject it for the first time. Ask your healthcare provider if you have any questions.

Keep this leaflet in case you need to look at it again later.

Important information for use of EGRIFTA®

- After mixing EGRIFTA® with Sterile Water for Injection, it should look clear and colorless, with no particles in it. Do not use EGRIFTA® if it looks cloudy, discolored, or if you see particles in it. Talk to your healthcare provider if you have any questions.
- Do not use EGRIFTA® after the date on the Medication Box and EGRIFTA® vial.
- Do not use a syringe or needle more than 1 time.
- **Do not share your EGRIFTA® needles with another person. You may give an infection to them or get an infection from them.**
- Sharing of needles can result in the transmission of infectious diseases, such as HIV. Do not share your EGRIFTA® syringe with another person, even if the needle is changed.
- If you are missing any supplies from your Medication Box or Injection Box, or if anything looks damaged call your pharmacist or contact THERA patient support™ toll-free 1-833-23-THERA (1-833-238-4372) right away.

Preparing for your EGRIFTA® injection

Step 1: Find a well-lit, clean, and flat surface, such as a table.

Step 2: Gather your supplies:

- Medication Box that contains 60 EGRIFTA® powder vials
- Injection Box that contains the following:
  a) 30 10-mL bottles of Sterile Water for Injection, used for mixing
  b) 30 sterile 3-mL syringes with sterile needle already attached
  c) 30 individual 1½" 18-gauge sterile needles, used for mixing
  d) 30 individual ½" 27-gauge injection needles

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- Other Supplies Needed
  - Alcohol pads
  - Sterile gauze
  - A "sharps container" or a puncture resistant container for throwing away used needles and syringes after you are done with them.

Material included in Injection Box (a, b, c, d) and Medication Box (e):

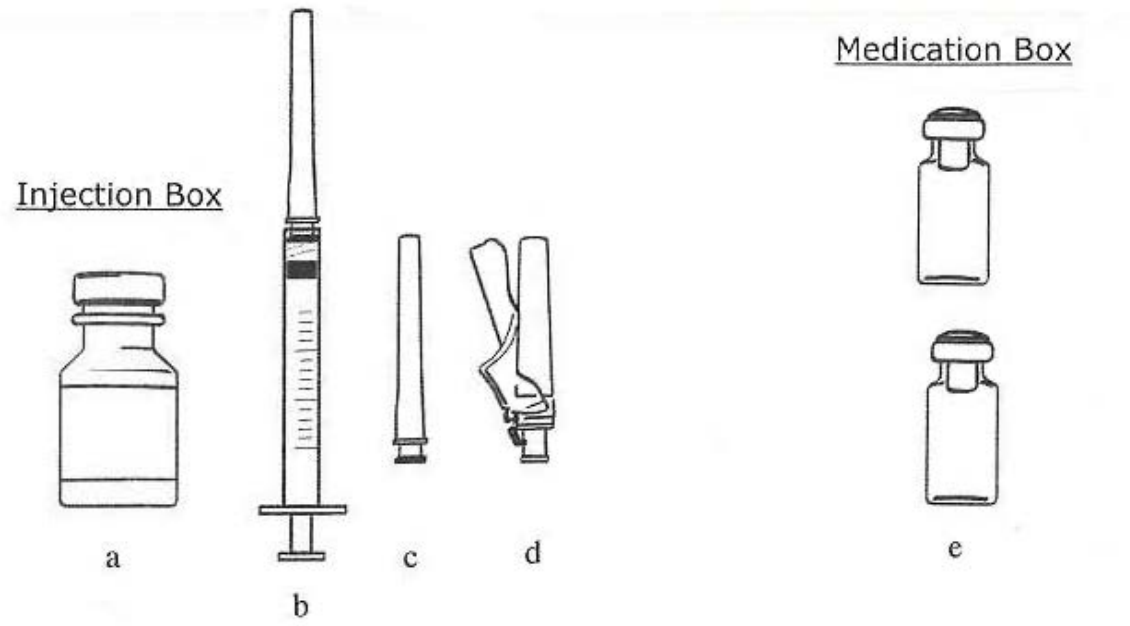

Figure A

Step 3: Take out the following from your Injection Box:

- A Sterile Water for Injection bottle (Figure A, a)
- A syringe with needle already attached (Figure A, b)
- A 1½" 18-gauge needle (Figure A, c)
- A ½" 27-gauge injection needle (Figure A, d)

Step 4: Take **2** EGRIFTA® vials (Figure A, e) from the Medication Box. Put the box with the remaining vials back in the refrigerator right away.

Step 5: Prepare to use your supplies:

- Wash your hands with soap and water. Dry your hands with a clean towel.
- Take off the plastic caps from the vials of EGRIFTA® and Sterile Water bottle.

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- Clean the rubber stoppers on top of the 2 vials of EGRIFTA® and Sterile Water bottle with an alcohol swab.

How to mix EGRIFTA®

Step 1: Pick up the syringe with needle attached (Figure A, b), remove the protective cap and insert the needle through the rubber stopper of the bottle of Sterile Water (Figure A, a; see Figure B for illustration). Turn both upside down, and pull back the plunger until the liquid reaches the 2.2 mL mark on the syringe. (See Figure C)

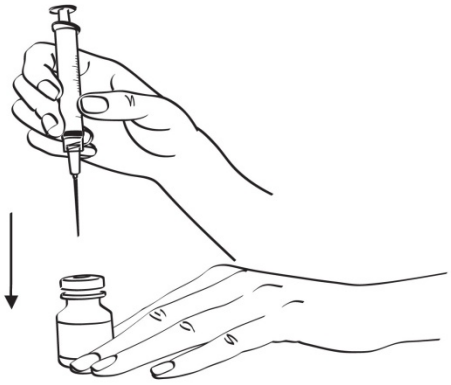

Figure B

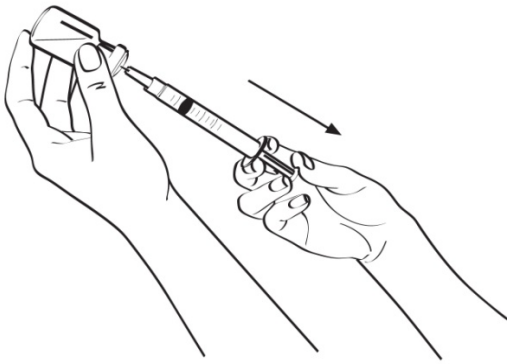

Figure C

Step 2: Take the syringe with needle attached out of the Sterile Water bottle and insert the needle into one of the EGRIFTA® vials. Push the plunger in slowly on a slight angle so water goes down the inside wall of the EGRIFTA® vial instead of directly onto the powder to avoid foaming. (See Figure D)

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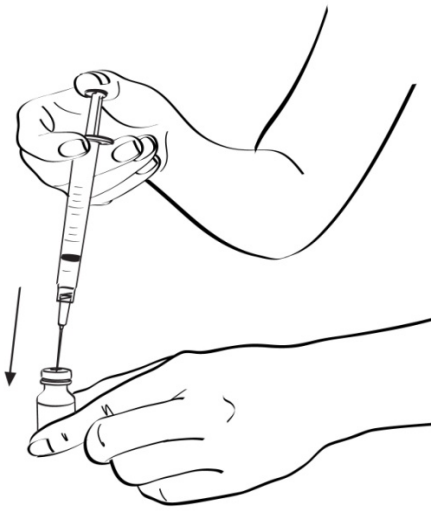

Figure D

Step 3: While keeping the syringe with needle attached in the vial and the vial upright, roll the vial gently in your hands for 30 seconds, until the Sterile Water and EGRIFTA® powder are mixed well. Do **not** shake the vial. (See Figure E)

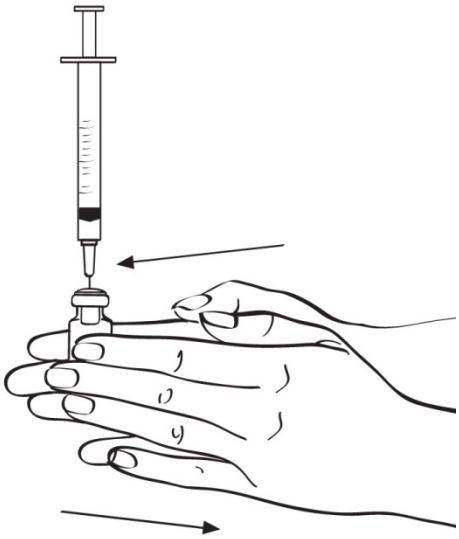

Figure E

Step 4: Still keeping the syringe with needle attached in the vial, turn both until the syringe is straight up. Pull down on the syringe until you see just the tip of the needle going through the rubber stopper, then pull back on the plunger until all

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the liquid inside the vial goes into the syringe. The level of medicine in the syringe should be around the 2.2 mL syringe mark. (See Figure F)

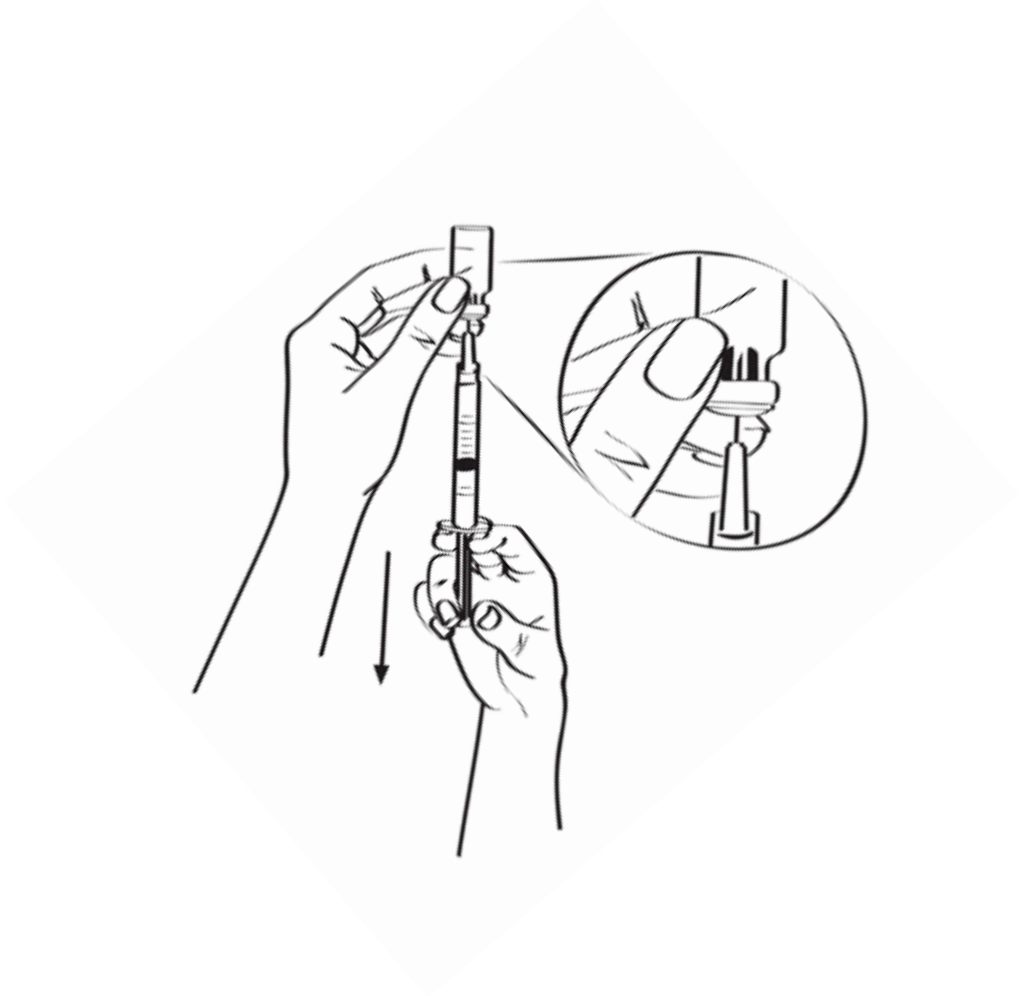

Figure F

Step 5: Take the needle out of the vial. (See Figure G)

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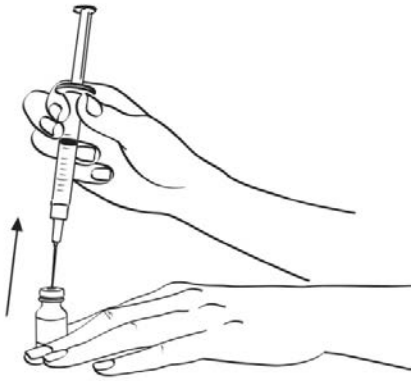

Figure G

Step 6: Place the needle cap on its side against a clean flat surface. Without touching the needle, hold the syringe and slide the needle carefully into the protective cap (See Figure H). Push the cap all the way or until it snaps shut (See Figure I). Do not touch the cap until it covers the needle completely.

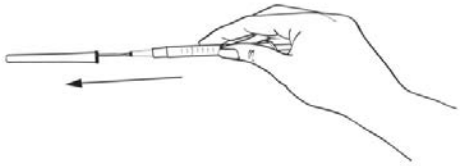

Figure H

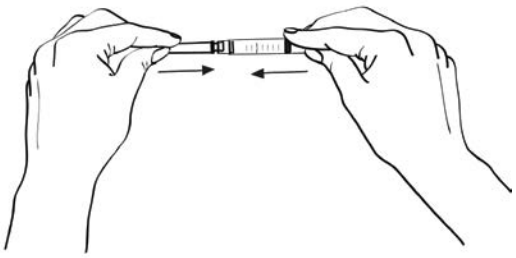

Figure I

Step 7: With the cap on the needle, remove the needle by holding the syringe firmly and twisting the cap counterclockwise (to the left). (See Figure J)

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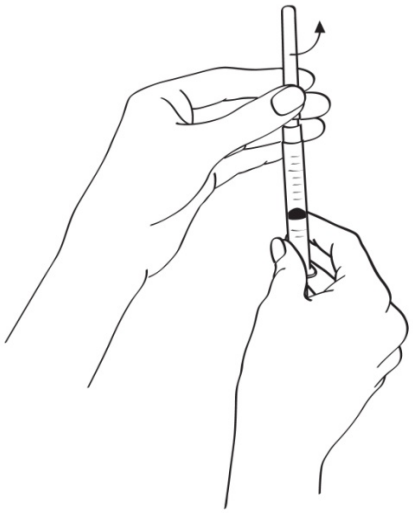

Figure J

Step 8: Place the 1½" 18-gauge mixing needle (Figure A, c), with its protective cap in place, onto the syringe. Twist the cap clockwise (to the right) until it is tight. (See Figure K)

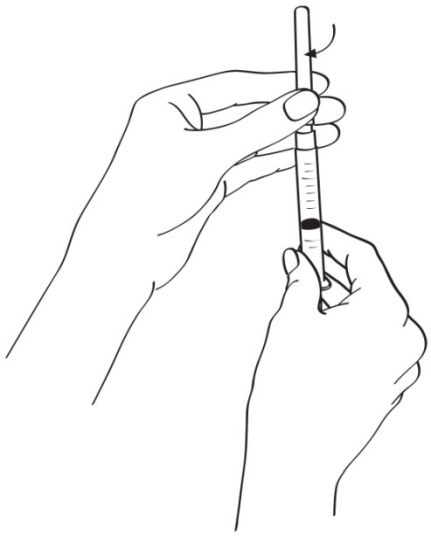

Figure K

Step 9: Remove the protective cap and insert the needle into the second *EGRIFTA*® vial (Figure A, e). Push the plunger in slowly on a slight angle so that

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the mixture goes down the inside wall of the EGRIFTA® vial instead of directly into the powder to avoid foaming (see Figure L).

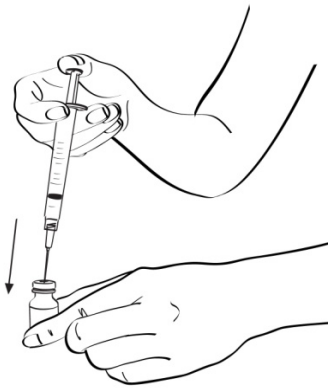

Figure L

Step 10: Keeping the syringe in the vial and the vial upright, roll the vial gently in your hands for 30 seconds, until the water and powder are mixed well. (Do **not** shake the vial.) The solution should look clear and colorless, with no particles in it. (See Figure M)

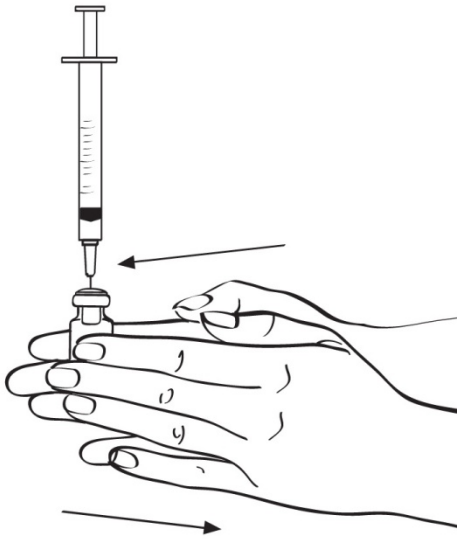

Figure M

Step 11: Still keeping the syringe in the vial, turn both until the syringe is straight up. Pull down on the syringe until you see just the tip of the needle going through the rubber stopper, then pull back on the plunger until all the liquid inside the vial

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goes into the syringe. The level of medicine in the syringe should be around the 2.2 mL syringe mark. (See Figure N)

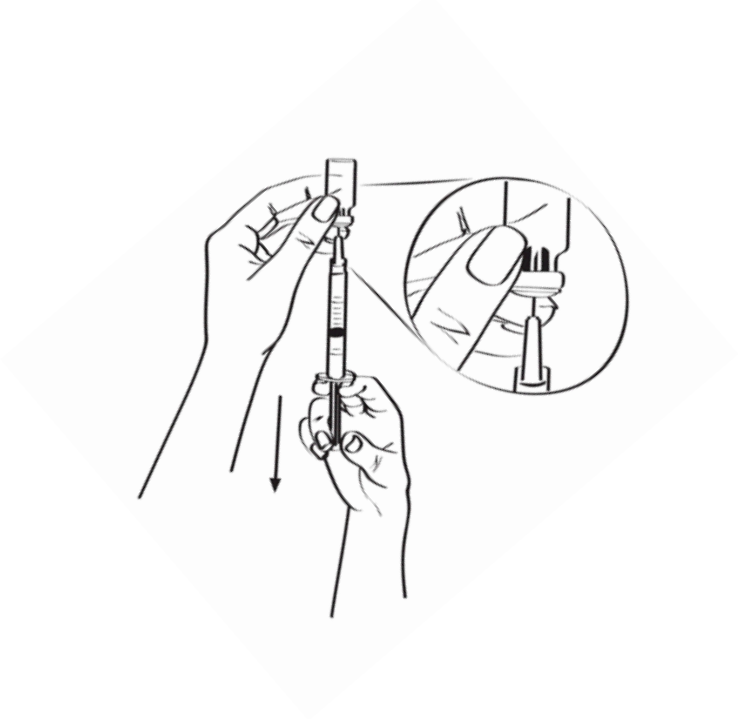

Figure N

Step 12: Take the needle out of the vial. (See Figure O)

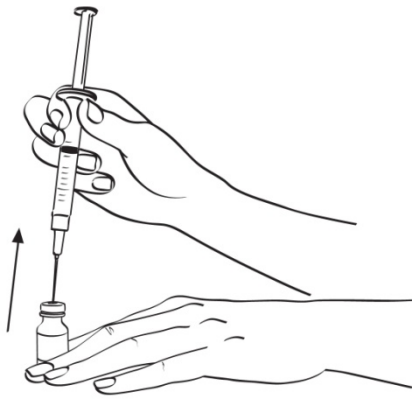

Figure O

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Step 13: Place the needle cap on its side against a clean flat surface. Without touching the needle, hold the syringe and slide the needle carefully into the protective cap (See Figure P). Push the cap all the way until it snaps shut (See Figure Q). Do not touch the cap until it covers the needle completely.

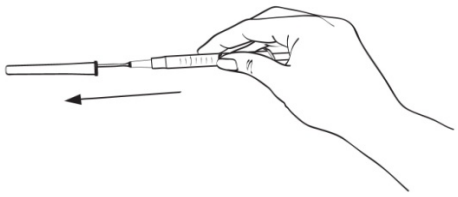

Figure P

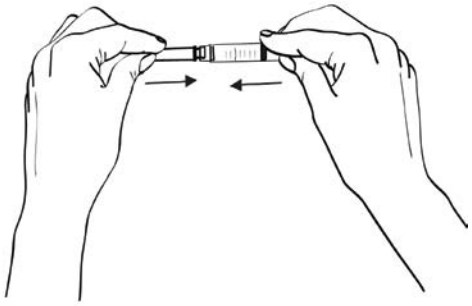

Figure Q

Step 14: With the needle cap on the needle, remove the mixing needle by holding the syringe firmly and twisting the cap counterclockwise (to the left). (See Figure R)

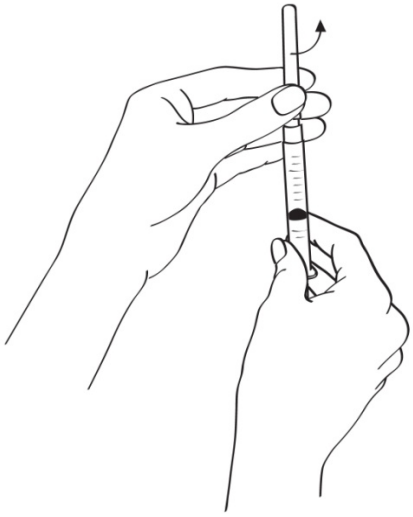

Figure R

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Step 15: Place the injection needle (Figure A, d), with its white protective cap in place, onto the syringe. Hold the syringe firmly and twist the cap clockwise (to the right) until it closes securely. (See Figure S)

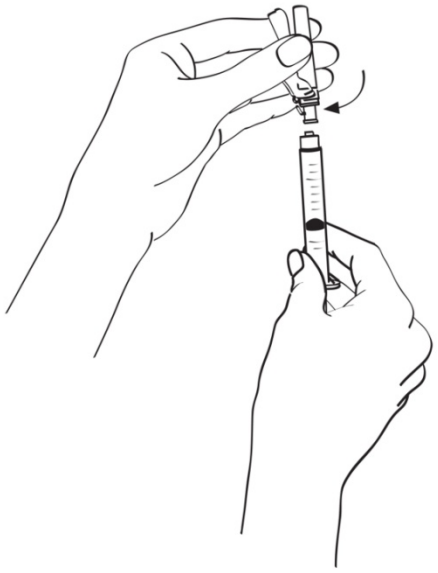

Figure S

Where do I inject EGRIFTA®?

You should inject EGRIFTA® into the skin on your stomach (abdomen). (See Figure T)

- Pick an injection site that is around your belly button to the left or right.
- Stay away from any area with scar tissue, bruises, reddening, infection, or irritation.
- Avoid areas with any hard bumps from previous injections.
- Change your injection site from one day to the next. This may help prevent bruising or irritation. You may want to keep a note of the date and location of each daily injection to help you remember.

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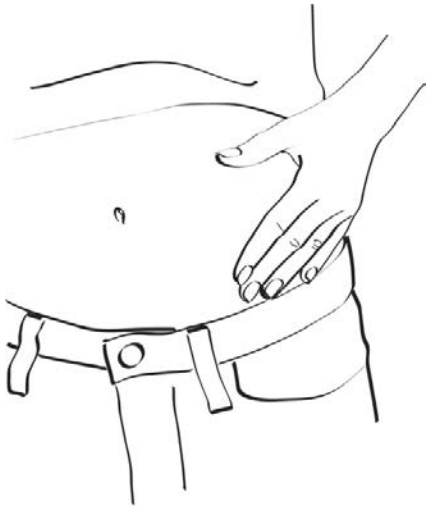

Figure T

How to inject EGRIFTA®

- Pick up the syringe and pull the cap straight off the injection needle. Do **not** twist it. (See Figure U)

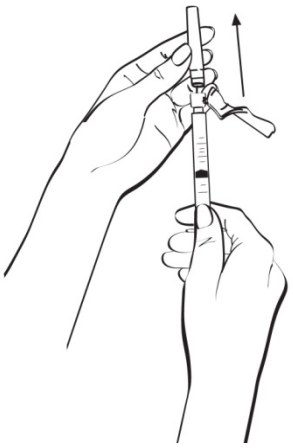

Figure U

- Tap the syringe gently with your finger to force any air bubbles to rise to the top. Press the plunger to push bubbles out. (See Figure V)

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Figure V

- Clean the injection site you have selected with an alcohol swab and let it dry. Hold the syringe in one hand. Use your other hand to hold a cleaned fold of skin for your injection. Hold the skin between your thumb and fingers. (See Figure W)

Figure W

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- Hold the syringe at a right angle to the skin, like a dart. Push the injection needle into the skin with a quick motion. Most of the needle should go beneath the skin surface. (See Figure X)

Figure X

- Remove your hand from the pinched area of skin after the needle goes in. Make sure the needle stays in the skin. (See Figure Y)

Figure Y

- Slowly push the plunger all the way down until all of the medicine in the syringe has been injected under the skin.
- Pull the injection needle out of your skin when the syringe is empty:
  - Be careful to pull it out at the same angle you put it in
  - Flip back the pink needle shield until it snaps, covering the injection needle completely. Keep pressing until you hear a click, that means the injection needle is protected. (See Figure Z)

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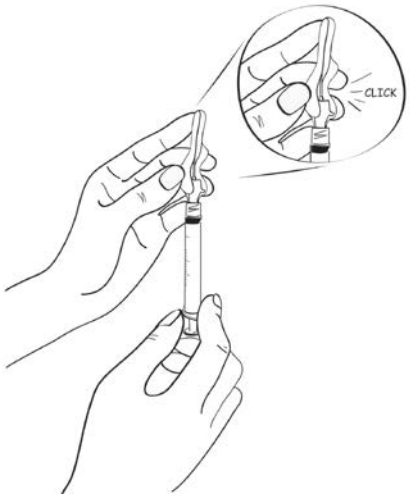

Figure Z

- Use a piece of sterile gauze to rub the injection site clean. If there is bleeding, apply pressure to the injection site with gauze for 30 seconds. If bleeding continues, apply a bandage to the site.

How should I dispose of the used syringes, needles, bottles and vials?

- **Do not** recap the needle or remove the needle from the syringe after you inject EGRIFTA®.
- Put your used EGRIFTA® needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps

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disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- If you accidentally prick another person with a used needle, that person should be informed to contact a healthcare provider right away about the accident.
- Keep the sharps container away from children and pets.

If you have any questions, call your healthcare provider. You can call THERA patient support™ toll-free 1-833-23-THERA (1-833-238-4372) or visit the EGRIFTA® Web site at: www.EGRIFTA.com for more information.

How do I store EGRIFTA®?

- EGRIFTA® has two boxes dispensed by the pharmacy:
  - Store the Medication Box of EGRIFTA® vials in the refrigerator between 2°C to 8°C (36°F to 46°F).
  - Store the Injection Box of Sterile Water for Injection, syringes and needles at room temperature between 20°C to 25°C (68°F to 77°F).
- Keep EGRIFTA® vials away from light.
- Do not freeze.
- After mixing, use EGRIFTA® right away and throw away any unused EGRIFTA®. Do not store mixed EGRIFTA®. Also, throw away the used bottle of Sterile Water for Injection.
- Do not use EGRIFTA® after the expiration date printed on the Medication Box and vial labels.

General information about the safe and effective use of EGRIFTA®.

Keep EGRIFTA® and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Jubilant HollisterStier General Partnership, 16751 Trans-Canada Highway, Montreal, Québec, Canada H9H 4J4

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

Revised: 07/2018

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EGRIFTA (2 mg/vial) safely and effectively. See full prescribing information for EGRIFTA (2 mg/vial).

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

RECENT MAJOR CHANGES

Dosage and Administration (2) 11/2018

INDICATIONS AND USAGE

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

Limitations of use:

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

DOSAGE AND ADMINISTRATION

- Two formulations and strengths are available for EGRIFTA. This Dosage and Administration information applies to the EGRIFTA 2 mg/vial (2.1).
- The dose of EGRIFTA is 1.4 mg (0.35 mL of the reconstituted solution) injected subcutaneously once daily. (2.1)
- Inject EGRIFTA into the abdomen, rotating injection sites. (2.1,5.6)
- Use only the diluent provided, Sterile Water for Injection, USP, to reconstitute EGRIFTA. (2.2)
- Reconstitute the vial of lyophilized powder with 0.5 mL of diluent. Mix by rolling the vial gently in your hands for 30 seconds. Do not shake. (2.2)
- Inspect the reconstituted vial visually for particulate matter and discoloration. Use only if the solution is clear, colorless and without particulate matter. (2.2)
- Administer 0.35 mL of EGRIFTA immediately following reconstitution and throw away any unused solution and diluent. (2.2)

DOSAGE FORMS AND STRENGTHS

- EGRIFTA for injection 2 mg single-dose vial with a diluent of 10 mL of Sterile Water for Injection, USP (3)

CONTRAINDICATIONS

EGRIFTA is contraindicated in patients with:

- Disruption of the hypothalamic-pituitary axis (4)
- Active malignancy (4)
- Known hypersensitivity to tesamorelin or excipients in EGRIFTA (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- *Increased risk of neoplasms:* Preexisting malignancy should be inactive and its treatment complete prior to starting EGRIFTA**.** Discontinue EGRIFTA if there is any evidence of recurrent malignancy. (5.1)
- *Elevated IGF-1:* EGRIFTA 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 therapy. Consider discontinuing in patients with persistent elevations. (5.2)
- *Fluid retention:* May occur with EGRIFTA and may include edema, arthralgia, and carpal tunnel syndrome. (5.3)
- *Glucose intolerance or diabetes mellitus:* May develop with EGRIFTA use. Evaluate glucose prior to and during therapy. (5.4)
- *Hypersensitivity reactions:* Have occurred in clinical trials. Advise patients to seek immediate medical attention and discontinue treatment if suspected. (5.5)
- *Increased mortality in patients with acute critical illness:* Consider discontinuation in critically ill patients**.** (5.7)

ADVERSE REACTIONS

Most commonly reported adverse reactions (>5%): 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 1-833-23THERA (1-833-238-4372) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

- *Cytochrome P450-metabolized drugs*: Monitor patients for potential interactions when administering with EGRIFTA. (7.1)
- *Glucocorticoids*: Patients receiving glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in maintenance or stress doses following initiation of EGRIFTA. (7.2)

USE IN SPECIFIC POPULATIONS

- *Lactation:* HIV-1 infected mothers should not breastfeed to avoid potential postnatal transmission of HIV-1. (8.2)

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

Revised: 11/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EGRIFTA is indicated for the reduction of excess abdominal fat in HIV-infected adult patients with lipodystrophy.

Limitations of Use:

- Long-term cardiovascular safety of EGRIFTA has not been established. Consider risk/benefit of continuation of treatment in patients who have not had a reduction in visceral adipose tissue.
- EGRIFTA 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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration

- Two formulations and strengths are available for EGRIFTA. This Dosage and Administration information only applies to EGRIFTA 2 mg/vial formulation.
- The dose of EGRIFTA is 1.4 mg, 0.35 mL of the reconstituted solution *[see Dosage and Administration (2.2)]*, injected subcutaneously once daily.
- Inject EGRIFTA into the abdomen. Rotate injection sites to different areas of the abdomen *[see Warnings and Precautions (5.5)]*. Do not inject into scar tissue, bruises or the navel.

2.2 Reconstitution Procedure

- Instruct patients to read the Instructions for Use enclosed in the EGRIFTA box.
- Use only the diluent provided, Sterile Water for Injection, USP, to reconstitute EGRIFTA.
- Reconstitute the vial of EGRIFTA lyophilized powder with 0.5 mL of diluent (2 mg per 0.5 mL). Mix by rolling the vial gently in your hands for 30 seconds. Do not shake.
- Inspect the reconstituted vial visually for particulate matter and discoloration. Use only if the solution is clear, colorless and without particulate matter.
- Administer 0.35 mL of EGRIFTA immediately following reconstitution and throw away any unused EGRIFTA solution and diluent. If not used immediately, discard the reconstituted EGRIFTA solution. Do not freeze or refrigerate the reconstituted EGRIFTA solution.

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3 DOSAGE FORMS AND STRENGTHS

EGRIFTA for injection is supplied in a single-dose 2 mg vial as a white to off-white lyophilized powder and a diluent of 10 mL of Sterile Water for Injection, USP.

4 CONTRAINDICATIONS

EGRIFTA is contraindicated in patients with:

- Disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma.
- Active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy *[see Warnings and Precautions (5.1)]*.
- Known hypersensitivity to tesamorelin or the excipients in EGRIFTA *[see Warnings and Precautions (5.5)]*.
- Pregnant women because modifying visceral adipose tissue offers no benefit in a pregnant woman and could result in fetal harm *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Neoplasms

New Malignancy

Carefully consider the decision to start treatment with EGRIFTA based on the increased background risk of malignancies in HIV-positive patients.

Active Malignancy

EGRIFTA induces the release of endogenous growth hormone (GH), a known growth factor. Do not treat patients with active malignancy with EGRIFTA *[see Contraindications (4)]*.

History of Malignancy

For patients with a history of non-malignant neoplasms, initiate EGRIFTA therapy after careful evaluation of the potential benefit of treatment. For patients with a history of treated and stable malignancies, initiate EGRIFTA therapy only after careful evaluation of the potential benefit of treatment relative to the risk of re-activation of the underlying malignancy. Discontinue EGRIFTA if there is any evidence of recurrent malignancy.

5.2 Elevated IGF-1 Levels

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

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Among patients who received EGRIFTA for 26 weeks, 47% had IGF-1 levels greater than 2 standard deviation scores (SDS), and 36% 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 34% had IGF-1 SDS >2 and 23% 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. This manifests as increased tissue turgor and musculoskeletal discomfort resulting in adverse reactions (e.g. edema, arthralgia, carpal tunnel syndrome) which are either transient or resolve with discontinuation of treatment.

5.4 Glucose Intolerance or Diabetes Mellitus

EGRIFTA treatment can result in glucose intolerance. During clinical trials, the percentages of patients with elevated HbA_{1c} (≥ 6.5%) from baseline to Week 26 were 5% and 1% 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 odds ratio of 3.3 (CI 1.4, 9.6)].

Evaluate glucose status prior to initiating EGRIFTA. Monitor all patients treated with EGRIFTA periodically to diagnose those who develop impaired glucose tolerance or diabetes. If patients treated with EGRIFTA develop glucose intolerance or diabetes, consider discontinuing EGRIFTA in patients who do not show a clear efficacy response.

EGRIFTA increases IGF-1, monitor patients with diabetes who are receiving treatment with EGRIFTA at regular intervals for potential development or worsening of retinopathy.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions occurred in 4% of patients treated with EGRIFTA in clinical trials. Reactions included pruritus, erythema, flushing, urticaria, and rash. In cases of suspected hypersensitivity reactions, advise patients to seek prompt medical attention and immediately discontinue treatment with EGRIFTA.

5.6 Injection Site Reactions

EGRIFTA may cause injection site reactions, including injection site erythema, pruritus, pain, irritation, and bruising. The incidence of injection site reactions was 25% in EGRIFTA-treated patients and 14% in placebo-treated patients during the first 26 weeks of treatment in clinical trials. Rotate injection sites to different areas of the abdomen to decrease injection site reactions *[see Dosage and Administration (2.1)]*.

5.7 Increased Mortality in Patients with 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 is a Growth Hormone-Releasing Hormone (GHRH) and since EGRIFTA stimulates growth hormone production, consider discontinuing EGRIFTA in critically ill patients.

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6 ADVERSE REACTIONS

The following important adverse reactions are also described elsewhere in the labeling:

- Increased risk of neoplasms *[see Warnings and Precautions (5.1)]*
- Elevated IGF-1 levels *[see Warnings and Precautions (5.2)]*
- Fluid retention *[see Warnings and Precautions (5.3)]*
- Glucose intolerance or diabetes mellitus *[see Warnings and Precautions (5.4)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.5)]*
- Injection site reactions *[see Warnings and Precautions (5.6)]*

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.

The safety of the EGRIFTA 2 mg/vial formulation has been established based on clinical trials conducted with the EGRIFTA 1 mg/vial formulation. Adverse reactions for the 1.4 mg dose (2 mg/vial formulation) of EGRIFTA are expected to be similar to those observed with the 2 mg dose (1 mg/vial formulation) of EGRIFTA *[see Clinical Pharmacology 12.3)]*.

Seven hundred and forty HIV-infected patients with lipodystrophy and excess abdominal fat were treated with EGRIFTA in clinical trials; of these, 543 received EGRIFTA during the initial 26-week placebo-controlled phase.

The most commonly reported adverse reactions were hypersensitivity reactions (e.g., rash, urticaria), edema-related reactions (e.g., arthralgia, extremity pain, peripheral edema, carpal tunnel syndrome), hyperglycemia, and injection site reactions (injection site erythema, pruritus, pain, urticaria, irritation, swelling, hemorrhage).

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.

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

Preferred Term	Placebo (N=263)	EGRIFTA (N=543)
Injection site reaction*	6	17
Arthralgia	11	13
Pain in extremity	5	6
Myalgia	2	6
Edema peripheral	2	6
Paresthesia	2	5
Hypoesthesia	2	4
Rash	2	4
Dysepsia	1	2
Musculoskeletal pain	1	2
Pain	1	2
Pruritus	1	2
Vomiting	0	3
Musculoskeletal stiffness	0	2
Blood creatine phosphokinase increased	0	1
Carpal tunnel syndrome	0	1
Joint swelling	0	1
Muscle strain	0	1
Night sweats	0	1
Palpitations	0	1

*Injection site reaction includes: Injection site erythema, Injection site pruritus, Injection site rash, Injection site urticaria, Injection site pain, Injection site swelling, Injection site irritation, Injection site hemorrhage.

In the EGRIFTA clinical trials, mean baseline HbA_{1c} was 5.3% among patients in both the EGRIFTA and placebo groups. Patients receiving EGRIFTA had an increased risk of developing diabetes (HbA_{1c} level ≥ 6.5%) compared with placebo (5% vs. 1%), with a hazard ratio of 3.3 (CI 1.4, 9.6).

6.2 Immunogenicity

As with all therapeutic proteins and peptides, there is a potential for development of anti- EGRIFTA 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.

In the clinical trials with the EGRIFTA 1 mg/vial formulation, anti-tesamorelin IgG antibodies were detected in 50% of patients treated with EGRIFTA for 26 weeks and 47% of patients who received EGRIFTA for 52 weeks. In the subset of patients with hypersensitivity reactions, anti-tesamorelin IgG antibodies were detected in 85%. 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. 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.

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Neutralizing antibodies to tesamorelin and hGHRH were detected in vitro at Week 52 in 10% and 5% of EGRIFTA-treated patients, respectively. Changes in VAT and IGF-1 levels in patients with or without in vitro neutralizing antibodies were comparable.

7 DRUG INTERACTIONS

7.1 Cytochrome P450-Metabolized Drugs

Co-administration of EGRIFTA with simvastatin, a CYP3A substrate, showed that EGRIFTA had no significant impact on the pharmacokinetics profiles of simvastatin in healthy subjects *[see Clinical Pharmacology (12.3)]*.

EGRIFTA stimulates GH production. Published data indicate that GH may modulate cytochrome P450 (CYP450) mediated antipyrine clearance. 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). Monitor patients for potential interactions when administering EGRIFTA in combination with other drugs known to be metabolized by CYP450 liver enzymes.

7.2 Glucocorticoids

GH inhibits 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. EGRIFTA stimulates GH production, therefore, patients receiving glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in maintenance or stress doses following initiation of EGRIFTA. Patients treated with cortisone acetate and prednisone may be affected more than others 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

Risk Summary

EGRIFTA is contraindicated in pregnant women because modifying visceral adipose tissue offers no benefit in pregnant women and could result in fetal harm *[see Clinical Considerations and Contraindications (4)]*. Administration of tesamorelin acetate to rats during organogenesis resulted in hydrocephaly in offspring at a dose of approximately two and four times the clinical dose, based on measured drug exposure (AUC). If EGRIFTA is used during pregnancy, or if the patient becomes pregnant while taking this drug, discontinue EGRIFTA.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk
During pregnancy, visceral adipose tissue increases due to normal metabolic and hormonal changes. Modifying pregnancy-associated physiologic changes in visceral adipose tissue with EGRIFTA offers no known benefit and could result in fetal harm.

Data

Animal Data
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. 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.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. There are no data on the presence of tesamorelin in human milk, the effects on the breastfed child, or the effects on milk production. Because of both the potential for (1) HIV-1 infection transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive patients), and (3) any possible adverse effects of EGRIFTA, mothers should not breastfeed if they receive EGRIFTA.

8.4 Pediatric Use

The safety and effectiveness of EGRIFTA in pediatric patients have not been established.

In pediatric patients with open epiphyses, treatment with EGRIFTA may result in linear growth acceleration and excessive growth. EGRIFTA is not indicated for use in pediatric patients with open or closed epiphyses.

8.5 Geriatric Use

There is no information on the use of EGRIFTA in patients greater than 65 years of age.

8.6 Renal Impairment

EGRIFTA has not been studied in patients with renal impairment.

8.7 Hepatic Impairment

EGRIFTA has not been studied in patients with hepatic impairment.

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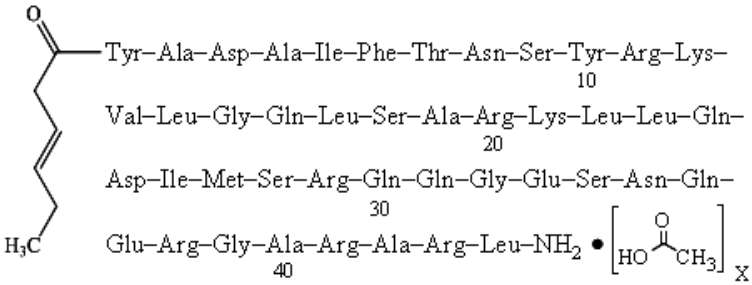
11 DESCRIPTION

EGRIFTA contains tesamorelin (as the acetate salt), a human growth hormone-releasing factor (GRF) analog. 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 $C_{221}H_{366}N_{72}O_{67}S \cdot x\ C_2H_4O_2$ ($x \approx 7$) 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-dose vial of EGRIFTA contains 2 mg of tesamorelin and the following inactive ingredients: 20 mg mannitol, USP, 10 mg sucrose, NF, 0.78 mg histidine, USP and 0.05 mg polysorbate 20, NF.

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 (GHRF), 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

Tesamorelin stimulates growth hormone secretion, and subsequently increases IGF-1 and IGFBP-3 levels. 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 patients receiving EGRIFTA in clinical trials.

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12.3 Pharmacokinetics

Absorption

The absolute bioavailability of EGRIFTA after subcutaneous administration of a 2 mg dose of EGRIFTA (1 mg/vial formulation) 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 using a 2 mg dose of EGRIFTA (1 mg/vial formulation). Tesamorelin mean extent of absorption (AUC) was 34% higher in HIV-infected patients than healthy subjects. Tesamorelin peak plasma concentration (C_{max}) was similar in HIV-infected patients and healthy subjects. The median peak plasma tesamorelin concentration (T_{max}) was 0.15 h in both populations.

Following single dose of subcutaneous administration of 1.4 mg of EGRIFTA (2 mg/vial formulation) in healthy subjects, the mean [coefficient of variation (CV)] $AUC_{0\text{-}inf}$ was 889.1 (57%) pg.h/mL. The mean (CV) C_{max} value was 2956.1 (47%) pg/mL and the median T_{max} was 0.15 h.

The systemic exposure (C_{max} and AUCs) of tesamorelin is similar between the 1.4 mg dose of EGRIFTA (2 mg/vial formulation) and the 2 mg dose of EGRIFTA (1 mg/vial formulation).

Distribution

The mean volume of distribution (±SD) of tesamorelin following a single subcutaneous administration of the 1.4 mg dose of EGRIFTA (2 mg/vial formulation) was 4.8 ± 1.9 L/kg in healthy subjects.

Metabolism

No formal metabolism studies have been performed in humans.

Elimination

Mean elimination half-life ($t_{1/2}$) of tesamorelin was 8 minutes in healthy subjects after single dose subcutaneous administration of the 1.4 mg of EGRIFTA (2 mg/vial formulation).

Specific Populations

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

Drug Interactions

Simvastatin

The effect of multiple dose administration of EGRIFTA on the pharmacokinetics of simvastatin and simvastatin acid was evaluated in healthy subjects. Co-administration with simvastatin (a 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 on the pharmacokinetics of ritonavir was evaluated in healthy subjects. Co-administration with ritonavir resulted in 9% decrease in AUC_{inf} and 11% decrease in C_{max} of ritonavir *[see Drug Interactions (7.1)]*.

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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.

14 CLINICAL STUDIES

The safety and effectiveness of the EGRIFTA 2 mg/vial formulation has been established based on adequate and well controlled studies with the EGRIFTA 1 mg/vial formulation, as well as a demonstration of comparable bioavailability between the 1.4 mg EGRIFTA dose (2 mg/vial formulation) and the 2 mg EGRIFTA dose (1 mg/vial formulation) *[see Clinical Pharmacology (12.3)]*.

Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in HIV-infected patients with lipodystrophy and excess abdominal fat (abdominal lipohypertrophy). Study 1 and Study 2 consisted of a 26-week Main Phase and a 26-week Extension Phase, respectively. Main inclusion criteria were age 18 to 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 mellitus, type 2 diabetes mellitus, previous treatment 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 a 2 mg dose of EGRIFTA (1 mg/vial formulation) 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 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 a 2 mg dose of EGRIFTA (1 mg/vial formulation) 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 (NCT 00123253)

This study randomized 412 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either a 2 mg dose of EGRIFTA (1 mg/vial formulation) (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

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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 (NCT 00435136)

This study randomized 404 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either a 2 mg dose of EGRIFTA (1 mg/vial formulation) (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% randomized to EGRIFTA and 40% randomized to placebo had impaired glucose tolerance, while 9% randomized to EGRIFTA and 10% randomized to placebo had diet-controlled type 2 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 2 and 3.

Table 2: 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	
	2 mg EGRIFTA (1 mg/vial) (N=273)	Placebo (N=137)	2 mg EGRIFTA (1 mg/vial) (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

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Table 3: 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	
		2 mg EGRIFTA (1 mg/vial) (N=273)	Placebo (N=137)	2 mg EGRIFTA (1 mg/vial) (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.

At Week 26, treatment with a 2 mg dose of EGRIFTA (1 mg/vial formulation) 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).

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.

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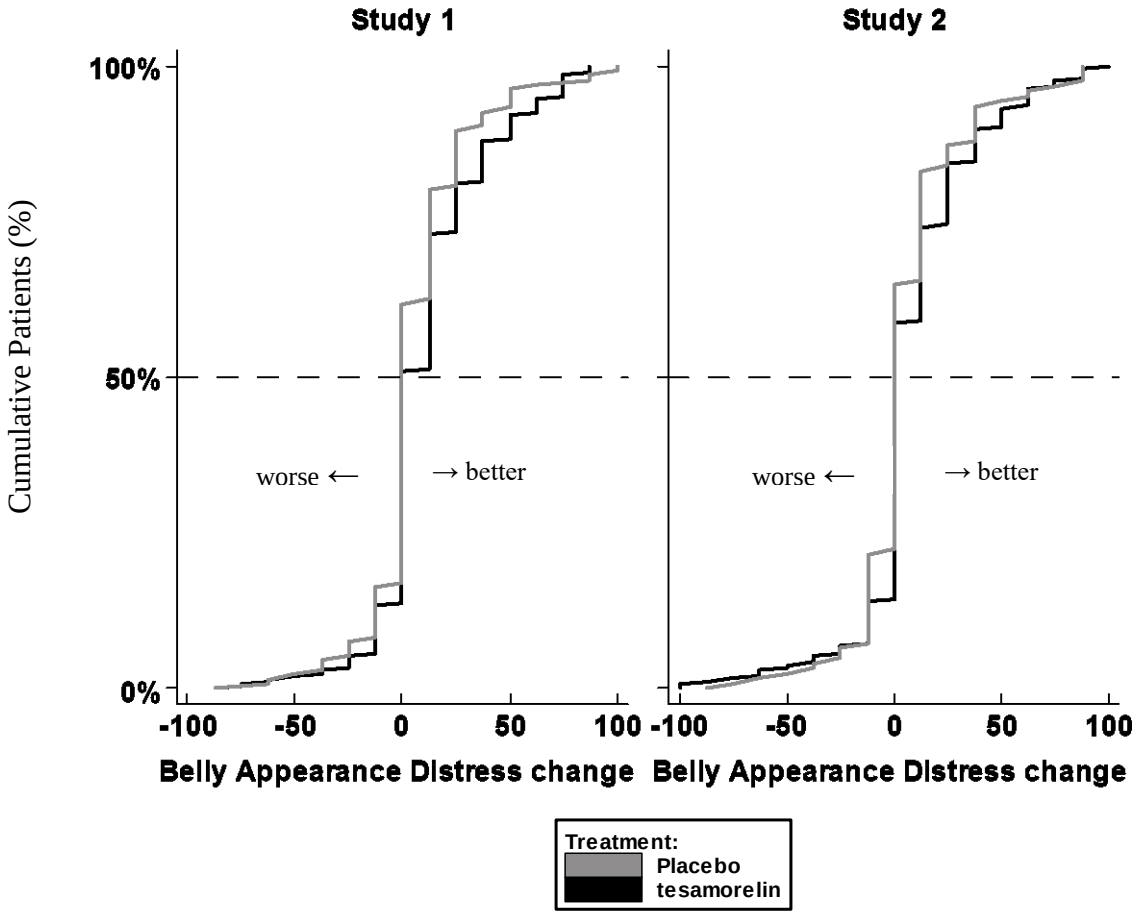
Figure 1. Cumulative Distribution of Response for Belly Appearance Distress



Extension Phase (Weeks 26-52):

In the double-blind Extension Phase, patients on a 2 mg dose of EGRIFTA (1 mg per vial formulation) completing the 26-week Main Phase were re-randomized to receive a 2 mg dose of EGRIFTA (1 mg per vial formulation) or placebo.

Study 1 (NCT 00123253)

This study re-randomized 207 HIV-infected patients with lipodystrophy who completed a 2 mg dose of EGRIFTA (1 mg/vial formulation) 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, 37% and 32%, respectively, had impaired glucose tolerance, while 2% re-randomized to EGRIFTA and 6% re-randomized to placebo had diet-controlled type 2 diabetes mellitus. The completion rate for patients randomized into the extension phase of Study 1 was 83%.

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Study 2 (NCT 00435136)

This study re-randomized 177 HIV-infected patients with lipodystrophy who completed EGRIFTA treatment in the Main Phase to receive either a 2 mg dose of EGRIFTA (1 mg/vial formulation) (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, 49% and 51%, respectively, had impaired glucose tolerance, while 4% re-randomized to EGRIFTA and 13% 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 4 and 5.

Table 4: 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.

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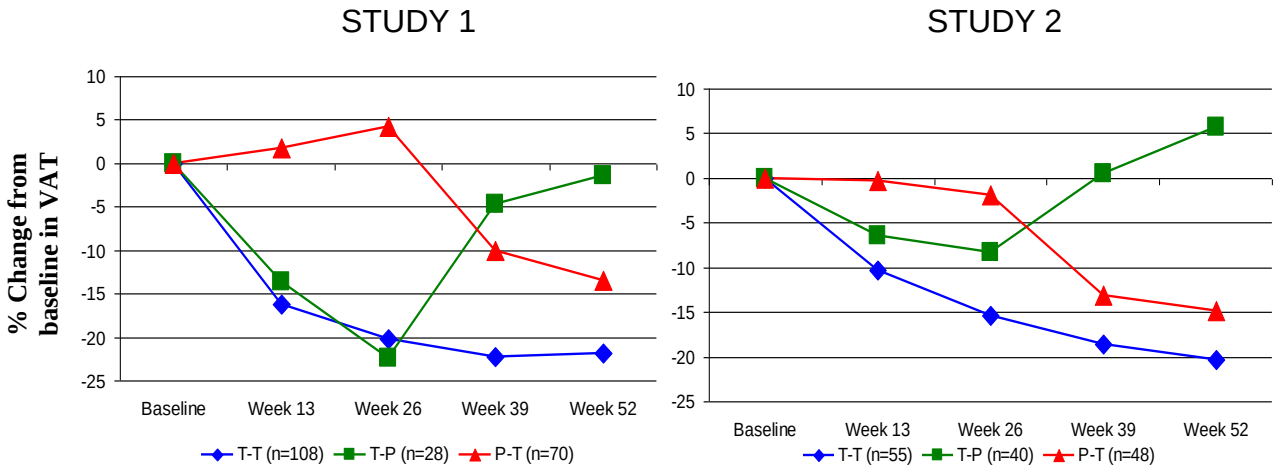
Figure 2. Percent Change from Baseline in VAT over Time



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.

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Table 5: 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 a 2 mg dose of EGRIFTA (1 mg/formulation) 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

EGRIFTA for injection is supplied as a white to off-white lyophilized powder in a 2 mg single-dose vial with a diluent of 10 mL vial of Sterile Water for Injection, USP.

EGRIFTA (NDC 62064-041-30) is available in a package comprised of two boxes, containing 30 (thirty) 2 mg single-dose vials of EGRIFTA in the medication box and 30 single-dose 10 mL bottles of Sterile Water for Injection, USP diluent with a 30-day supply of disposable syringes and needles in the injection box.

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Protect EGRIFTA from light and keep in the original box until time of use. Store EGRIFTA 2 mg/vial up to 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Store the Sterile Water for Injection, USP, syringes and needles at controlled room temperature of 20°C to 25°C (68°F to 77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Increased Risk of Malignancy

Inform patients about the increased background risk of malignancies in HIV-positive patients and for patients with a history of neoplasms, inform them about the risk of malignancy reoccurrence *[see Warnings and Precautions (5.1)]*.

Elevated IGF-1 Levels

Inform patients that treatment with EGRIFTA increases IGF-1 levels and that they will need periodic monitoring of their IGF-1 levels *[see Warnings and Precautions (5.2)]*.

Fluid Retention

Inform patients that treatment with EGRIFTA may cause fluid retention, resulting in adverse reactions including edema, arthralgia, and carpal tunnel syndrome *[see Warnings and Precautions (5.3)]*.

Glucose Intolerance or Diabetes Mellitus

Inform patients that treatment with EGRIFTA may result in glucose intolerance or diabetes mellitus. Advise patients that they will need to be monitored to see if impaired glucose tolerance or diabetes mellitus develops, and that if they have pre-existing diabetes mellitus, they may need adjustments to their anti-diabetic medications *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Inform 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 if a reaction occurs *[see Warnings and Precautions (5.5)]*.

Injection Site Reactions

Inform patients that injection site reactions may occur with EGRIFTA, including injection site erythema, pruritus, pain, irritation, and bruising. Advise patients to rotate the site of injection to reduce the risk of injection site reactions *[see Warnings and Precautions (5.6)]*.

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)]*.

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Lactation

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 breastfeed *[see Use in Specific Populations (8.2)]*.

Administration

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.

EGRIFTA® is a registered trademark of Theratechnologies Inc.

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

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PATIENT INFORMATION
EGRIFTA® (eh-GRIF-tuh)
(tesamorelin for injection)
for subcutaneous use
2 mg vial

Read the Patient Information that comes with EGRIFTA before you start to take EGRIFTA and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is EGRIFTA?

- EGRIFTA is an injectable prescription medicine to reduce the excess in belly fat in HIV-infected adult patients. EGRIFTA is a growth hormone-releasing factor (GHRF).

The long term safety of EGRIFTA on the heart and blood vessels (cardiovascular) is not known.

EGRIFTA is not for weight loss management.

It is not known whether taking EGRIFTA **helps improve how well you take antiretroviral medicines.**

It is not known if EGRIFTA is safe and effective in children.

EGRIFTA is not recommended to be used in children with open or closed bone growth plates (epiphyses).

Who should not use EGRIFTA?
Do not take EGRIFTA if you:

- have pituitary gland tumor, pituitary gland surgery, other problems related to your pituitary gland, or have had a head injury.
- have active cancer. Any previous cancer should be inactive and any previous cancer treatment should be complete before starting EGRIFTA.
- are allergic to tesamorelin or any of the ingredients in EGRIFTA. See the end of this leaflet for a complete list of ingredients in EGRIFTA.
- are pregnant or plan to become pregnant. EGRIFTA can harm your unborn baby. If you become pregnant, stop using EGRIFTA and talk with your healthcare provider.

What should I tell my healthcare provider before using EGRIFTA?
Before using EGRIFTA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had cancer.
- have problems with your blood sugar or diabetes. Some people with diabetes who use EGRIFTA may develop or may have worsening eye problems.
- have scheduled heart or stomach surgery.
- are breastfeeding or plan to breastfeed. It is not known if EGRIFTA passes into your breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers **not** breastfeed to avoid the risk of passing HIV infection to your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking EGRIFTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use EGRIFTA?

- **Read the detailed "Instructions for Use"** that comes with EGRIFTA before you start using it. Your healthcare provider will show you how to inject EGRIFTA.
- Use EGRIFTA exactly as your healthcare provider tells you to use it.
- Inject EGRIFTA under the skin (subcutaneously) of your belly (abdomen).
- Change (rotate) the injection site on your belly (abdomen) with each dose. Do not inject EGRIFTA into scar tissue, bruises or your belly button.
- **Do not share your EGRIFTA syringe or needles with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.**

What are the possible side effects of EGRIFTA?
EGRIFTA may cause serious side effects, including:

- **may increase risk of new cancer in HIV positive patients or your cancer coming back (reactivation).** Stop using EGRIFTA if you have any cancer symptoms come back.
- **increased levels of your insulin-like growth factor-1 (IGF-1).** Your healthcare provider will do blood tests to check your IGF-1 levels while you are taking EGRIFTA.
- **swelling (fluid retention).** EGRIFTA can cause swelling in some parts of your body. Call your healthcare provider if you have an increase in joint pain or pain or numbness in your hands or wrist (carpal tunnel syndrome).
- **increase in blood sugar (glucose) or diabetes.** Your healthcare provider will check your blood sugar from time to time.

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- **serious allergic reaction.** Some people taking EGRIFTA may have an allergic reaction. **Stop using EGRIFTA and get emergency help right away if you have any of the following symptoms:**
  - a rash over your body
  - hives
  - swelling of your face or throat
  - shortness of breath or trouble breathing
  - fast heartbeat
  - feeling of faintness or fainting
- **injection site reactions.** Change (rotate) your injection site to help lower your risk for injection site reactions. Call your healthcare provider for medical advice if you have the following symptoms around the area of the injection site:
  - redness
  - itching
  - pain
  - irritation
  - bleeding
  - rash
  - swelling
- increased risk of death in people who have critical illnesses because of heart or stomach surgery, trauma or serious breathing (respiratory) problems has happened when taking certain amounts of growth hormone.

The most common side effects of EGRIFTA include:

- joint pain
- pain in legs and arms
- swelling in your legs
- muscle pain

These are not all the possible side effects of EGRIFTA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800- FDA-1088.

You may also report side effects to T · THERA patient support toll-free at 1-833-23THERA (1-833-238-4372).

How should I store EGRIFTA 2 mg vial?

- EGRIFTA comes in two boxes given to you by the pharmacy.
  - Store the Medication Box of 2 mg EGRIFTA vials at room temperature between 68°F to 77°F (20°C to 25°C).
  - Store the Injection Box of Sterile Water for Injection, syringes and needles at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep EGRIFTA vials in the box and out of the light.
- After mixing, use EGRIFTA right away and throw away any unused EGRIFTA.
- Do not store, freeze or refrigerate after EGRIFTA has been mixed with the sterile water.
- Throw away the used bottle of Sterile Water for Injection.
- Do not use EGRIFTA after the expiration date printed on the carton and vial labels.

Keep EGRIFTA and all medicines out of the reach of children.

General information about the safe and effective use of EGRIFTA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EGRIFTA for a condition for which it was not prescribed. Do not give EGRIFTA to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about EGRIFTA that is written for healthcare professionals.

What are the ingredients in EGRIFTA?

Active ingredient: tesamorelin

Inactive ingredients: mannitol, sucrose, histidine, polysorbate 20

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For more information about EGRIFTA, go to www.EGRIFTA.com or contact toll-free at 1-833-23THERA (1-833-238-4372).

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 11/2018

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Instructions for Use

EGRIFTA® (eh-GRIF-tuh)
(tesamorelin for injection)
for subcutaneous use
2 mg vial

This Instructions for Use (IFU) contains step-by-step information on how to use the **2 mg vial** of EGRIFTA. **Each 2 mg vial** of EGRIFTA must be mixed with **0.5 mL of the Sterile Water for Injection** provided in the Injection Box given to you by the pharmacy. **You only need one** EGRIFTA 2 mg **vial from the Medication Box** to complete your dose. The recommended **dose is 1.4 mg (0.35 mL).**

Be sure that you read, understand, and follow this IFU before using EGRIFTA. Your healthcare provider should show you how to mix and inject EGRIFTA before you inject it for the first time. Ask your healthcare provider if you have any questions.

Keep this IFU in case you need to look at it again later.

Important information for use of EGRIFTA

- After mixing EGRIFTA with Sterile Water for Injection, it should look clear and colorless, with no particles in it. Do not use EGRIFTA if it looks cloudy, discolored, or if you see particles in it. Talk to your healthcare provider if you have any questions.
- Do not use EGRIFTA after the expiration date on the EGRIFTA vials.
- Do not use a syringe or needle more than 1 time.
- **Do not share your EGRIFTA syringe or needles with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.**
- If you are missing any supplies from the boxes given to you by the pharmacy or if anything looks damaged call your pharmacist or contact THERA patient support™ toll-free at 1-833-23THERA (1-833-238-4372) right away.

Preparing for your EGRIFTA injection

Step 1: Find a well-lit, clean, and flat surface, such as a table.

Step 2: Gather your supplies:

- Medication Box that contains 30 EGRIFTA 2 mg vials
- Injection Box that contains the following:
  a) 30 single-dose 10-mL bottles of Sterile Water for Injection, used for mixing
  b) 60 sterile 1-mL syringes
  c) 60 sterile individual 1" 20-gauge needles, used for mixing
  d) 30 sterile individual ½" 30-gauge needles, used for injection
- Other Supplies Needed
  - Alcohol pads

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- Sterile gauze
- A "sharps container" or a puncture resistant container for throwing away used needles and syringes after you are done with them.

Material included in Injection Box (a, b, c, d) and Medication Box (e) for the EGRIFTA 2 mg vial:

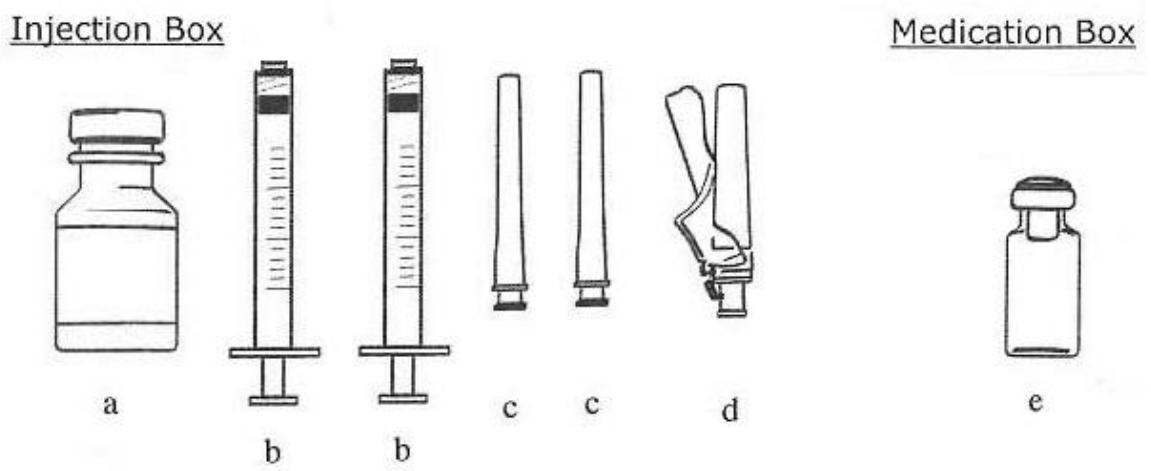

Figure A

Step 3: Take out the following from the Injection Box:

- A Sterile Water for Injection bottle (Figure A, a)
- Two 1-mL syringes (Figure A, b)
- Two 1" 20-gauge needles used for mixing (Figure A, c)
- A ½" 30-gauge needle used for injection (Figure A, d)

Step 4: Take 1 EGRIFTA 2 mg vial (Figure A, e) from the Medication Box.

Step 5: Prepare to use your supplies:

- Wash your hands with soap and water. Dry your hands with a clean towel.
- Take off the plastic caps from the vial of EGRIFTA and Sterile Water bottle.
- Clean the rubber stoppers on top of the vial of EGRIFTA and Sterile Water bottle with an alcohol pad

How to mix EGRIFTA 2 mg vial

Step 1: Place the 1" 20-gauge needle used for mixing (Figure A, c), with its white protective cap in place, onto the syringe (Figure A, b). Hold the syringe firmly and twist the cap clockwise (to the right) until it closes securely. (See Figure B)

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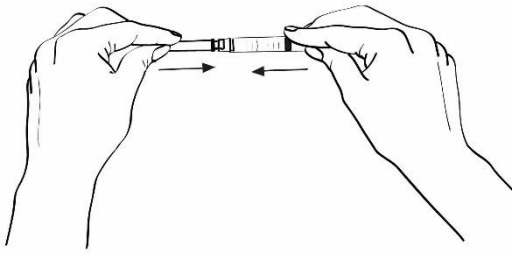

Figure B

Step 2: Remove the protective cap and insert the needle through the rubber stopper of the bottle of Sterile Water (Figure A, a. See Figure C for illustration). Turn the bottle and syringe upside down, pull back the plunger until the liquid reaches the 0.5 mL mark on the syringe, and throw away the bottle containing the unused Sterile Water. (See Figure D)

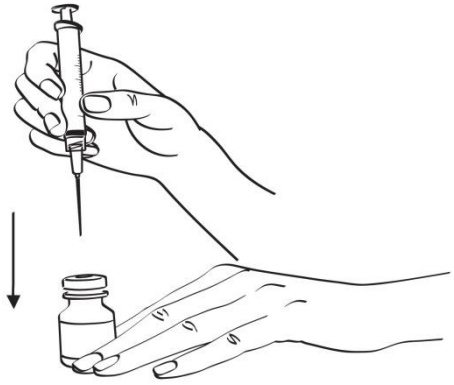

Figure C

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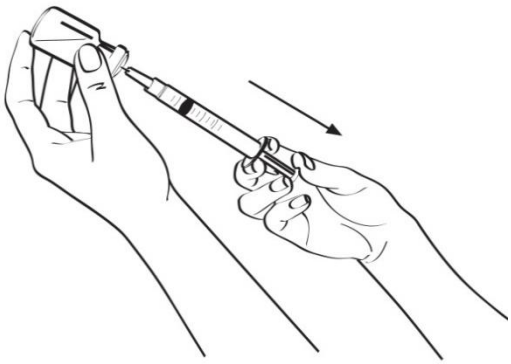

Figure D

Step 3: Take the syringe with needle attached out of the Sterile Water bottle and insert the needle into the EGRIFTA vial. Push the plunger in slowly on a slight angle so water goes down the inside wall of the EGRIFTA vial instead of directly onto the powder to avoid foaming. (See Figure E)

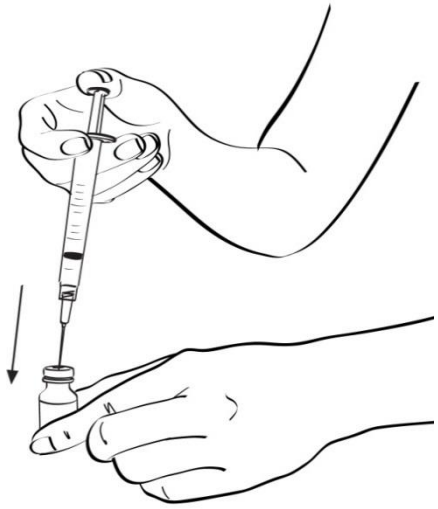

Figure E

Step 4: Take the needle out of the vial and throw away the syringe and needle. (See Figure F and see section **How should I dispose of the used syringes, needles, bottles and vials?**).

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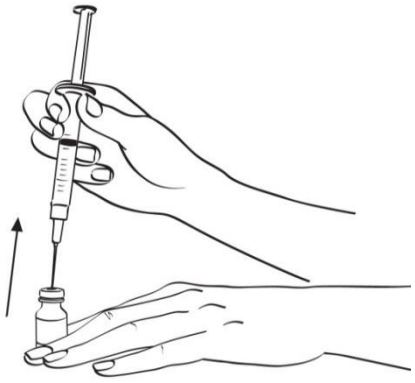

Figure F

Step 5: Roll the vial gently in your hands for 30 seconds, until the Sterile Water and EGRIFTA powder are mixed well. Do **not** shake the vial. (See Figure G)

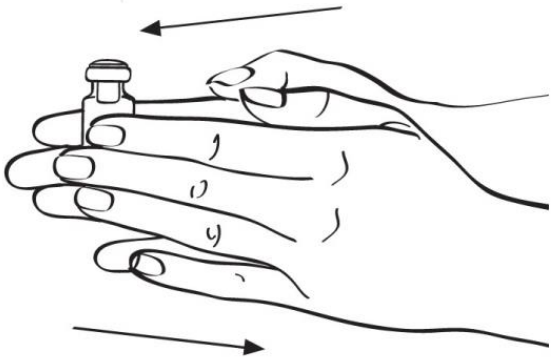

Figure G

Step 6: Place a new unused 1" 20-gauge needle used for mixing (Figure A, c), with its white protective cap in place, onto a new unused syringe (Figure A, b). Hold the syringe firmly and twist the cap clockwise (to the right) until it closes securely. (See Figure H)

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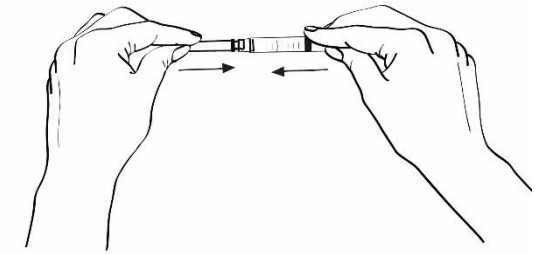

Figure H

Step 7: Remove the protective cap and insert the needle into the EGRIFTA vial (Figure A, a. See Figure I for illustration). Turn the bottle and syringe upside down and pull down on the syringe until you see just the tip of the needle going through the rubber stopper, then pull back on the plunger until all the liquid inside the vial goes into the syringe. The level of medicine in the syringe should be around the 0.4 mL syringe mark. (See Figure J)

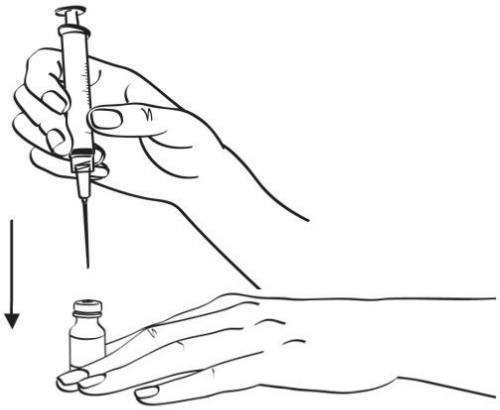

Figure I

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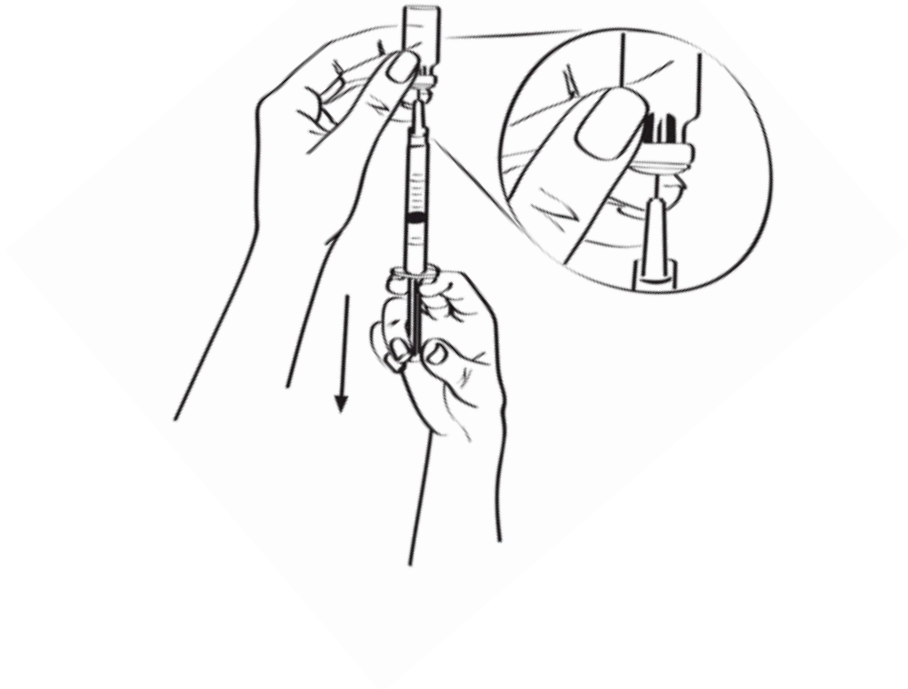

Figure J

Step 8: Take the needle out of the vial. (See Figure K)

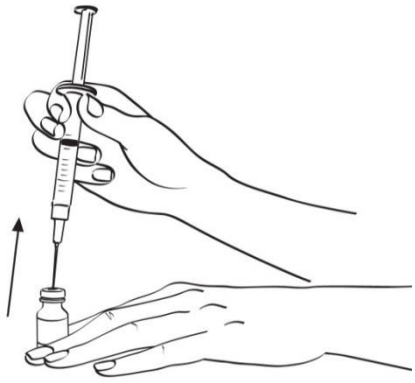

Figure K

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Step 9: Place the needle cap on its side against a clean flat surface. Without touching the needle, hold the syringe and slide the needle carefully into the protective cap (See Figure L). Push the cap all the way or until it snaps shut (See Figure M). Do not touch the cap until it covers the needle completely.

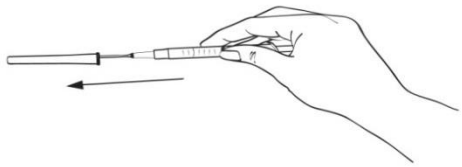

Figure L

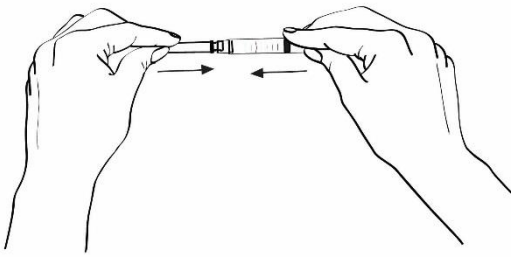

Figure M

Step 10: With the cap on the needle, remove the needle by holding the syringe firmly and twisting the cap counterclockwise (to the left). (See Figure N)

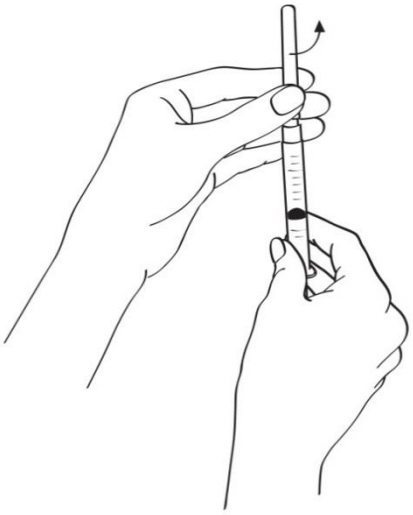

Figure N

Step 11: Place a ½" 30-gauge needle used for injection (Figure A, d), with its white protective cap in place, onto the syringe. Hold the syringe firmly and twist the cap clockwise (to the right) until it closes securely. (See Figure O)

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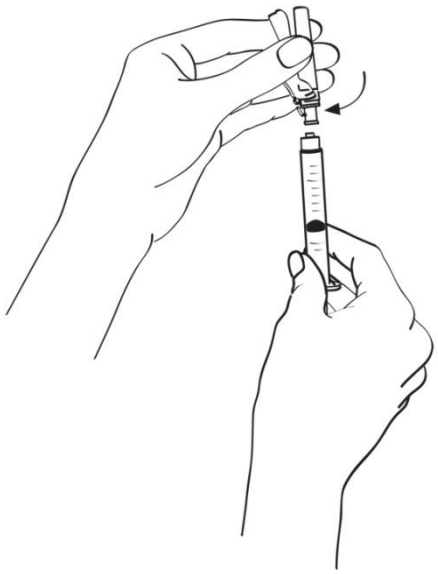

Figure O

Where do I inject EGRIFTA 2 mg vial?

You should inject EGRIFTA into the skin on your belly (abdomen). (See Figure P)

- Pick an injection site that is around your belly button to the left or right.
- Stay away from any area with scar tissue, bruises, reddening, infection, or irritation.
- Avoid areas with any hard bumps from previous injections.
- Change your injection site around the belly button from one day to the next. This may help prevent bruising or irritation. You may want to keep a note of the date and location of each daily injection to help you remember.

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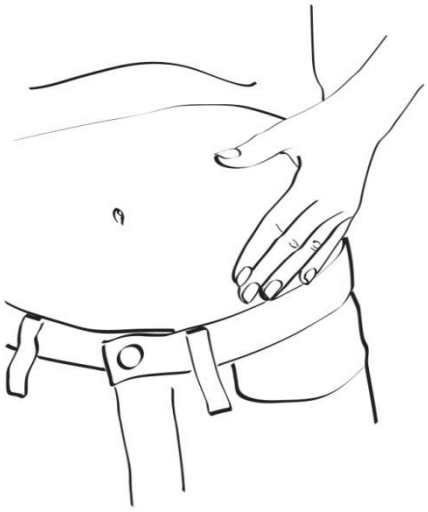

Figure P

How to inject EGRIFTA

- Pick up the syringe and pull the cap straight off the injection needle. Do **not** twist it. (See Figure Q)

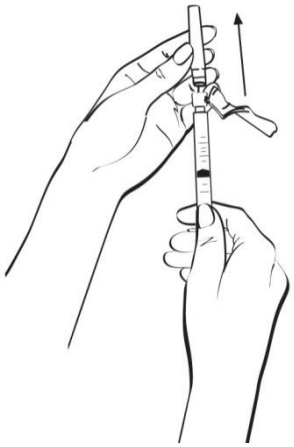

Figure Q

- Tap the syringe gently with your finger to force any air bubbles to rise to the top. Press the plunger to push bubbles out and adjust the volume to the 0.35 mL mark. (See Figure R)

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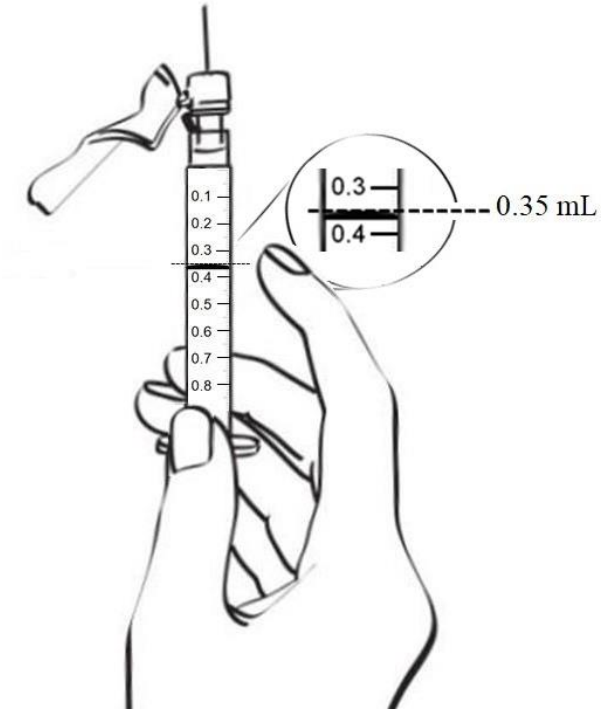

Figure R

- Clean the injection site you have selected with an alcohol pad and let it dry. Hold the syringe in one hand. Use your other hand to hold a cleaned fold of skin for your injection. Hold the skin between your thumb and fingers. (See Figure S)

Figure S

- Hold the syringe at a right angle to the skin, like a dart. Push the injection needle into the skin with a quick motion. Most of the needle should go beneath the skin surface. (See Figure T)

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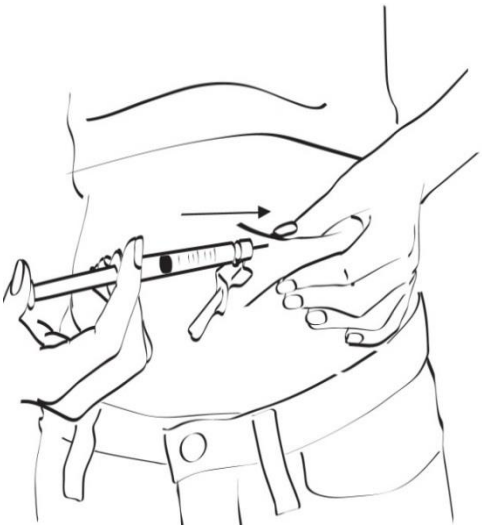

Figure T

- Remove your hand from the pinched area of skin after the needle goes in. Make sure the needle stays in the skin. (See Figure U)

Figure U

- Slowly push the plunger all the way down until all of the medicine in the syringe has been injected under the skin.
- Pull the injection needle out of your skin when the syringe is empty:
  - Be careful to pull it out at the same angle you put it in.
  - Flip back the pink needle shield until it snaps, covering the injection needle completely. Keep pressing until you hear a click that means the injection needle is protected. (See Figure V)

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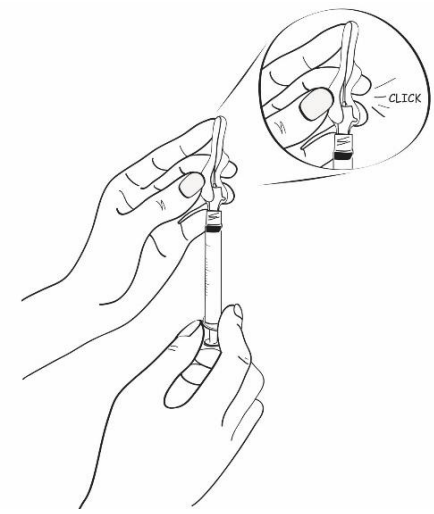

Figure V

- Use a piece of sterile gauze to rub the injection site clean. If there is bleeding, apply pressure to the injection site with gauze for 30 seconds. If bleeding continues, apply a bandage to the site.

How should I dispose of the used syringes, needles, bottles and vials?

- **Do not** recap the needle or remove the needle from the syringe after you inject EGRIFTA.
- Put your used EGRIFTA needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and pens. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- If you accidentally prick another person with a used needle, that person should be informed to contact a healthcare provider right away about the accident.
- Keep the sharps container away from children and pets.

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If you have any questions, call your healthcare provider. You can call THERA patient support™ toll-free 1-833-23THERA (1-833-238-4372) or visit the EGRIFTA® website at: www.EGRIFTA.com for more information.

How do I store EGRIFTA 2 mg vial?

- EGRIFTA comes in two boxes given to you by the pharmacy:
  - Store the Medication Box of 2 mg EGRIFTA vials at room temperature between 68°F to 77°F (20°C to 25°C).
  - Store the Injection Box of Sterile Water for Injection, syringes and needles at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep EGRIFTA vials in the box and out of the light.
- After mixing, use EGRIFTA right away and throw away any unused EGRIFTA.
- Do not store, freeze or refrigerate EGRIFTA after it has been mixed with the sterile water.
- Throw away the used bottle of Sterile Water for Injection.
- Do not use EGRIFTA after the expiration date printed on the carton and vial labels.

General information about the safe and effective use of EGRIFTA.

Keep EGRIFTA and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

THERA technologies

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