HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

EGRIFTA SV 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 SV 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 SV. (1)

DOSAGE AND ADMINISTRATION

- The recommendations in this prescribing information only apply to EGRIFTA SV (tesamorelin) for injection 2 mg per vial formulation. For recommendations for tesamorelin for injection 1 mg per vial formulation, see the EGRIFTA prescribing information. These two formulations and strengths have differences in the dosage, the number of vials required to prepare a dose, reconstitution instructions, and storage requirements. (2.1).
- The dose of EGRIFTA SV is 1.4 mg (0.35 mL of the reconstituted solution) injected subcutaneously once daily. (2.1)
- Inject EGRIFTA SV into the abdomen, rotating injection sites. (2.1,5.6)
- Use only the diluent provided, Sterile Water for Injection, to reconstitute EGRIFTA SV. (2.2)
- Reconstitute one 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 SV immediately following reconstitution and throw away any unused solution and diluent. (2.2)

DOSAGE FORMS AND STRENGTHS

- For injection: 2 mg in a single-dose vial with a diluent of 10 mL of Sterile Water for Injection (3)

CONTRAINDICATIONS

EGRIFTA SV is contraindicated in:

- Patients with disruption of the hypothalamic-pituitary axis (4)
- Patients with active malignancy (4)
- Patients with known hypersensitivity to tesamorelin or excipients in EGRIFTA SV (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- *Increased risk of neoplasms:* Preexisting malignancy should be inactive and its treatment complete prior to starting EGRIFTA SV**.** Discontinue EGRIFTA SV if there is any evidence of recurrent malignancy. (5.1)
- *Elevated IGF-1:* EGRIFTA SV stimulates GH production and increases serum IGF-1, a growth factor. The effects of prolonged elevations in IGF-1 levels are unknown Monitor IGF-1 levels during EGRIFTA SV therapy. Consider discontinuing in patients with persistent elevations. (5.2)
- *Fluid retention:* May occur with EGRIFTA SV and may include edema, arthralgia, and carpal tunnel syndrome. (5.3)
- *Glucose intolerance or diabetes mellitus:* May develop with EGRIFTA SV 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 SV. (7.1)
- *Glucocorticoids*: Patients receiving glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in maintenance or stress doses following initiation of EGRIFTA SV. (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: 02/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage and Administration
2.2 Reconstitution Procedure
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Risk of Neoplasms
5.2 Elevated IGF-1 Levels
5.3 Fluid Retention
5.4 Glucose Intolerance or Diabetes Mellitus
5.5 Hypersensitivity Reactions
5.6 Injection Site Reactions
5.7 Increased Mortality in Patients with Acute Critical Illness
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
7 DRUG INTERACTIONS
7.1 Cytochrome P450-Metabolized Drugs
7.2 Glucocorticoids
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.6 Immunogenicity
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EGRIFTA SV 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 SV has not been established. Consider risk/benefit of continuation of treatment in patients who have not had a reduction in visceral adipose tissue.
- EGRIFTA SV is not indicated for weight loss management as it has a weight neutral effect.
- There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA SV.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration

- The dosage and administration recommendations in this prescribing information only apply to EGRIFTA SV (tesamorelin) for injection 2 mg per vial formulation. For dosage and administration recommendations for tesamorelin for injection 1 mg per vial formulation, see the EGRIFTA prescribing information. These two formulations and strengths have differences in the dosage, the number of vials required to prepare a dose, reconstitution instructions, and storage requirements.
- The dose of EGRIFTA SV is 1.4 mg, 0.35 mL of the reconstituted solution *[see Dosage and Administration (2.2)]*, injected subcutaneously once daily.
- Inject EGRIFTA SV 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 SV Medication Box.
- Use only the diluent provided, Sterile Water for Injection, to reconstitute EGRIFTA SV.
- Reconstitute 1 vial of EGRIFTA SV 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.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if the solution is clear, colorless and without particulate matter.
- Administer 0.35 mL of EGRIFTA SV immediately following reconstitution and throw away any unused solution and diluent. If not used immediately, discard the reconstituted solution. Do not freeze or refrigerate the reconstituted solution.

3 DOSAGE FORMS AND STRENGTHS

For injection: 2 mg of tesamorelin as a white to off-white lyophilized powder in a single-dose vial and a diluent of 10 mL of Sterile Water for Injection.

4 CONTRAINDICATIONS

EGRIFTA SV is contraindicated in:

- Patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation or head trauma.
- Patients with active malignancy. Any preexisting malignancy should be inactive and its treatment

complete prior to instituting therapy *[see Warnings and Precautions (5.1)]*.

- Patients with known hypersensitivity to tesamorelin or the excipients in EGRIFTA SV *[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 SV based on the increased background risk of malignancies in HIV-positive patients.

Active Malignancy

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

History of Malignancy

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

5.2 Elevated IGF-1 Levels

EGRIFTA SV stimulates GH production and increases serum IGF-1, a growth factor. The effects of prolonged elevations in IGF-1 levels are unknown. Monitor IGF-1 levels during EGRIFTA SV therapy. Consider discontinuing EGRIFTA SV in patients with persistent elevations of IGF-1 levels (e.g., >3 SDS), particularly if the efficacy response is not robust.

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 SV 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, and carpal tunnel syndrome) which are either transient or resolve with discontinuation of treatment.

5.4 Glucose Intolerance or Diabetes Mellitus

EGRIFTA SV treatment can result in glucose intolerance. During clinical trials, the percentages of patients with elevated HbA_{1c} ($\geq$ 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 $\geq$ 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 SV. Monitor all patients treated with EGRIFTA SV periodically to diagnose those who develop impaired glucose tolerance or diabetes. If patients treated with

EGRIFTA SV develop glucose intolerance or diabetes, consider discontinuing EGRIFTA SV in patients who do not show a clear efficacy response.

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

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 SV.

5.6 Injection Site Reactions

EGRIFTA SV treatment 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 SV is a growth hormone-releasing hormone (GHRH) and since it stimulates growth hormone production, consider discontinuing EGRIFTA SV in critically ill patients.

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 EGRIFTA SV (2 mg/vial formulation) has been established based on clinical trials conducted with EGRIFTA (1 mg/vial formulation). Adverse reactions for the 1.4 mg dose (2 mg/vial formulation) of EGRIFTA SV 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 (740) 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, and carpal tunnel syndrome), hyperglycemia, and injection site reactions (injection site erythema, pruritus, pain, urticaria, irritation, swelling, and 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.

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
Dyspepsia	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).

7 DRUG INTERACTIONS

7.1 Cytochrome P450-Metabolized Drugs

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

EGRIFTA SV 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, and cyclosporine). Monitor patients for potential interactions when administering EGRIFTA SV 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 SV 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 SV. 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 SV 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 SV is used during pregnancy, or if the patient becomes pregnant while taking it, discontinue EGRIFTA SV.

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% to 4% and 15% to 20%, respectively.

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 SV 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 tesamorelin, mothers should not breastfeed if they receive EGRIFTA SV.

8.4 Pediatric Use

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

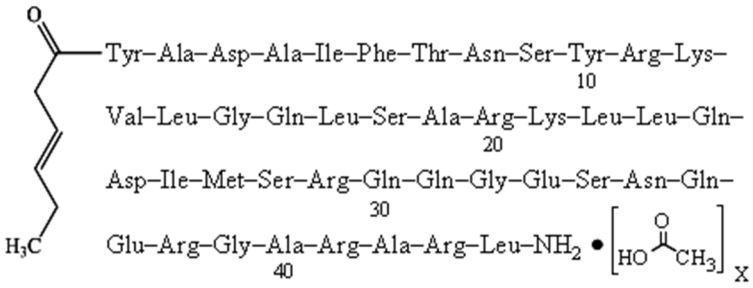
In pediatric patients with open epiphyses, treatment with EGRIFTA SV may result in linear growth acceleration and excessive growth. EGRIFTA SV is not indicated for use in pediatric patients with open or closed epiphyses.

8.5 Geriatric Use

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

11 DESCRIPTION

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



EGRIFTA SV (tesamorelin) for injection is a sterile, white to off-white, preservative-free lyophilized powder for subcutaneous injection. Each single-dose vial of EGRIFTA SV contains tesamorelin 2 mg (equivalent to approximately 2.2 mg of tesamorelin acetate) and the following inactive ingredients: 0.78 mg histidine, USP, 20 mg mannitol, USP, 0.05 mg polysorbate 20, NF and 10 mg sucrose, NF. Hydrochloric acid may be used to adjust the pH. The pH of EGRIFTA SV is between 4.5 and 7.4. After reconstitution with 0.5 mL of Sterile Water for Injection, resultant concentration is 2 mg/0.5 mL and the solution is clear and colorless.

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.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of tesamorelin 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 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 SV (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 SV (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 SV (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 SV (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)]*.

12.6 Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of the anti-drug antibodies in other studies, including those of EGRIFTA SV or other growth hormone-releasing factor analog.

In the clinical trials with the EGRIFTA 1 mg/vial formulation, anti-tesamorelin IgG antibodies were detected in 50% of patients who received 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.

Neutralizing antibodies to tesamorelin and human GHRH (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.

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 EGRIFTA SV (2 mg/vial formulation) has been established based on adequate and well controlled studies with EGRIFTA (1 mg/vial formulation), as well as a demonstration of comparable bioavailability between the 1.4 mg EGRIFTA SV 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 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	-31 (-39,-24)		-21 (-29,-12)	

MAIN PHASE (Baseline-Week 26)				
	Study 1		Study 2	
difference (95% CI)				
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 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).

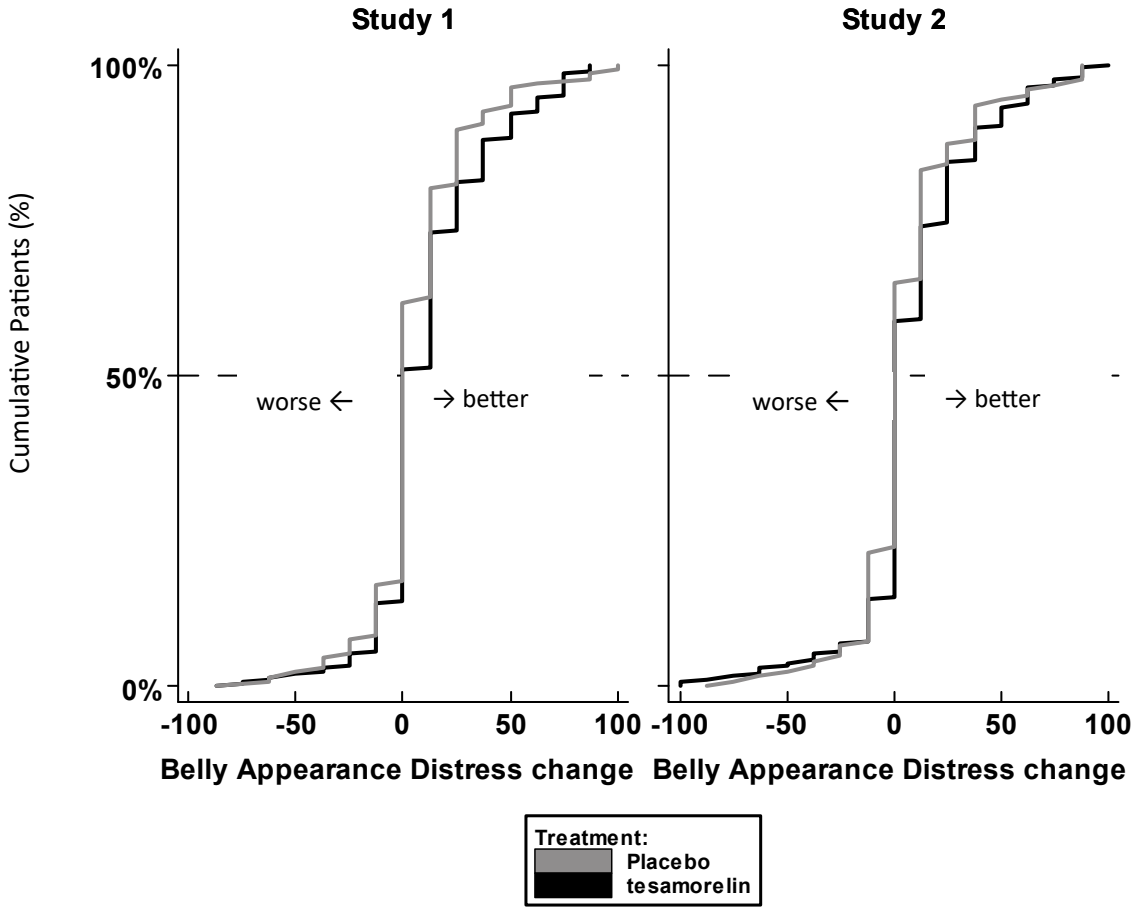
Patient Reported Outcomes

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.

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/vial formulation) completing the 26-week Main Phase were re-randomized to receive a 2 mg dose of EGRIFTA (1 mg/ 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%.

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.

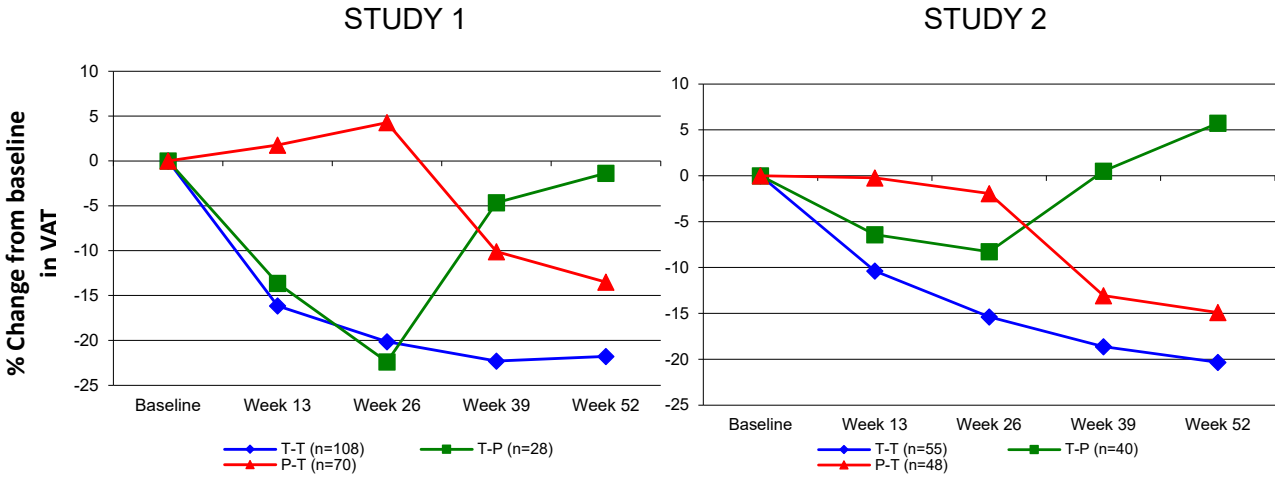
[1]T-T = tesamorelin for Weeks 0-26 and tesamorelin for Weeks 26-52

[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.

Figure 2. Percent Change from Baseline in VAT over Time



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

Table 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 SV (tesamorelin) 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.

EGRIFTA SV (NDC 62064-241-30) is available in a package comprised of two boxes, containing 30 (thirty) 2 mg single-dose vials of EGRIFTA SV in the Medication Box and 30 single-dose 10 mL bottles of Sterile Water for Injection diluent with a 30-day supply of disposable syringes and needles in the Injection Box.

Store EGRIFTA SV 2 mg vial at room temperature at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect EGRIFTA SV from light by keeping in the original box until time of use. Store the Injection box (containing Sterile Water for Injection, syringes and needles) at room temperature at 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 SV 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 SV 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 SV 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 SV. Advise patients to seek prompt medical attention and to immediately discontinue treatment with EGRIFTA SV if a reaction occurs *[see Warnings and Precautions (5.5)].*

Injection Site Reactions
Inform patients that injection site reactions may occur with EGRIFTA SV, 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 SV if pregnancy occurs, as the drug offers no known benefit to pregnant women and could result in fetal harm *[see Contraindications (4) and Use in Specific Populations (8.1)].*

Lactation
Because of both the potential for HIV-1 infection transmission and serious adverse reactions in nursing infants, mothers receiving EGRIFTA SV should be instructed not to breastfeed *[see Use in Specific Populations (8.2)]*.

Administration
Counsel patients that they should never share an EGRIFTA SV 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.

Manufactured by Theratechnologies Inc., 2015 Peel Street, Suite 1100, Montréal, Québec, Canada H3A 1T8

US License No. 2091 for Theratechnologies Inc.