Drug Use Research & Management Program
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Month/Year of Review: April 2012
Generic Name: Tesamorelin
PDL Class: Synthetic growth hormone-releasing factor analog
Dossier received: Yes

End date of literature search: January 31, 2012
Brand Name (Manufacturer): Theratechnologies, Inc.
Comparator Therapies: None

EXECUTIVE SUMMARY:

FDA Approved Indications: Tesamorelin is a growth hormone releasing factor (GRF) analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.[1]

Background/Reason for Review: Patients with human immunodeficiency virus (HIV) taking antiretroviral therapy frequently develop increased visceral adiposity, dyslipidemia, and insulin resistance, which may be associated with increased cardiovascular risk. Studies have shown that growth hormone-releasing hormone (GHRH) has shown positive changes in fat distribution in HIV-infected patients.[1, 2] Tesamorelin is a synthetic growth hormone-releasing factor analog that has been approved for the use of HIV infected patients with lipodystrophy. This review will evaluate the available evidence of efficacy, safety, and tolerability to further define its role in therapy and to identify potential parameters for use.

Issues/Key questions:
Is tesamorelin effective and safe for the treatment of excess abdominal fat in HIV-infected patients?
Does treatment with tesamorelin result in improved health outcomes?

Efficacy: There were two, Phase 3, randomized, controlled studies that evaluated the efficacy of tesamorelin compared to placebo; both studies conducted an initial 26-week phase and a 26-week extension phase to evaluate long-term safety.[7-9] Both studies saw a significant change in visceral adipose tissue (VAT) in patients treated with tesamorelin (-15.2% and -10.9%) compared to placebo (+5.0% and -0.6%, $p<0.001$ for both trials). Secondary efficacy endpoints from the extension phases indicate that this decrease in VAT is not maintained after treatment discontinuation. There was limited reduction in body mass index or waist circumference after 26 weeks after treatment with tesamorelin.

Safety: Patients receiving tesamorelin experienced a higher rate of adverse events compared to those in the placebo group.[1] The most common adverse events were headache, arthralgias, injection-site bruising, diarrhea, peripheral edema, myalgia, and limb pain. Contraindications to tesamorelin include those with active malignancy, hypersensitivity to tesamorelin and/or mannitol, pregnancy, and patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, or pituitary tumor/surgery, head irradiation or head trauma. The long term safety and potential long term cardiovascular benefit of tesamorelin is unknown.[1]

Conclusions/Evidence Grade: Strength of evidence is moderate. Clinical trials were generally well designed and show that tesamorelin is associated with a statistically significant decrease in visceral adipose tissue, the clinical significance of which is unclear. There is no evidence to show that a decrease in visceral adipose tissue is associated with improved medication adherence, morbidity or mortality in HIV-infected patients with lipodystrophy. Tesamorelin also requires daily subcutaneous administration and the effect is not maintained following discontinuation.

Recommendations: Require a prior authorization for approved OHP diagnoses only.

BACKGROUND/CURRENT LANDSCAPE:

Highly active antiretroviral therapies (HAART) are considered the standard of care in HIV-infected patients who require treatment. Treatment with HAART has clearly demonstrated significant reductions in HIV-associated morbidity and mortality but is not without adverse effects. Patients receiving treatment with HAART, and especially protease inhibitors, are at high risk for development of HIV-associated lipodystrophy, which is characterized by changes in lipid composition, insulin resistance, diabetes mellitus, and fat redistribution.[3-6] There is no standardized definition for diagnosing HIV-associated lipodystrophy, so estimations of its prevalence range from 5-83% of patients using protease inhibitors. Disease prevalence for patients using nucleoside reverse transcriptase inhibitors is not available.

The long-term implications of lipodystrophy are not known, but there is concern that an increase lipid abnormalities is linked to an increase in the risk of cardiovascular disease. There have been some studies that suggest there is a relationship between the degree of coronary artery disease and the amount of visceral fat deposition, but none of these studies were conducted in HIV-positive patients using HAART, and many of the studies included patients who had additional risk factors for cardiovascular disease (e.x. diabetes, impaired glucose tolerance, hypercholesterolemia). Nonetheless, there is no clear association between lipodystrophy in HIV-infected patients and cardiovascular disease. [1, 3-6]

Until the approval of tesamorelin, there was no FDA-approved treatment for lipodystrophy in HIV-infected patients. Patients who developed intolerable fat distribution may have been switched to an alternative HAART regimen. Hypertriglyceridemia may be treated with a fibrate or peroxisome proliferator-activated receptor (PPAR) agonist. GHRH has lipolytic properties and studies have shown positive changes in fat distribution in HIV-infected patients, however any improvement seen on fat distribution was reversed upon discontinuation of growth hormone. Tesamorelin is a synthetic growth hormone-releasing factor analog that has been approved for the use of HIV infected patients with lipodystrophy.[1]

CLINICAL PHARMACOLOGY:

Tesamorelin acts on pituitary cells in the brain to stimulate the synthesis and release of endogenous growth hormone, causing increases in insulin-like growth factor I and insulin-like growth factor binding protein 3.[1]

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1) Mortality

2) Major cardiovascular events

3) Compliance with anti-retroviral therapy measured by the proportion of days covered (PDC) ratio.

4) Rate of treatment related adverse events

Study Endpoints:

1) Primary endpoint: Percent change in the visceral adipose tissue (VAT) from baseline to week 26.
2) Percent change in insulin-like growth factor 1 (IGF-I)
3) Body image – determined by questionnaire in which subjects rate their belly size, belly image distress, and belly profile.
4) Percent change in biochemical indices – Lipid levels [triglycerides, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol], glucose, insulin and free testosterone.

Extension phase:

1) Primary endpoint was safety
2) Secondary efficacy endpoints: 52-week efficacy endpoints (% change in VAT, IGF-I, biochemical indices and body image survey scores).

Evidence Table

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH[3]	Quality Rating[4]; Comments
1.Falutz 2007[7,8] RCT, DB, PC, MC	1. Tesamorelin 2mg SQ daily 2. Placebo	HIV+ patients stable on ART for ≥ 8 weeks with evidence of abdominal fat accumulation defined as a waist circumference of ≥ 95 cm and a waist-to-hip ratio of ≥ 0.94 for men and a waist circumference of ≥ 94 cm and a waist-to-hip ratio of ≥0.88 for women. More patients in the tesamorelin group had received non-nucleoside reverse-transcriptase inhibitors (53.7 vs 41.6, p=0.03) **Exclusion Criteria:** Type 1 or 2 diabetes, serum creatinine >1.5, elevated liver enzymes, history of malignancy, untreated hypothyroidism or hypertension	N=412 Randomized 2:1, tesamorelin:placebo (PBO) Tx: n=275 PBO: n=137 Extension Phase (randomized 3:1) T-T: n=154 T-P: n=50	RCT – 26 weeks Extension phase (6 months) – subjects who remained in the trial for the extension phase were re-randomized 3:1 t receive tesamorelin or placebo.	• **% Δ VAT** Tx: -15.2% PBO: 5.0% Diff -32.9%, 95% CI (-40.7 to -25) p<0.001 • **% Δ IGF-I** Tx:81 PBO:-5.0 Diff: 125; 95% CI (105 to 146) p<0.001 • **% Δ Total cholesterol** Tx: -3.3 PBO: -0.7 p=0.02 • **% Δ fasting glucose** Tx: 3.7 PBO: 1.6 p=0.28 EXTENSION PHASE • **% Δ VAT** T-T: 17.5% p<0.001 T-P: 1.3% p=0.432	NA NA NA NA NA NA	% patients experiencing any AE: Tx: 82.8 PBO:75.2 p=0.09 % patients experience treatment-related AE: Tx: 53.8 PBO: 36.5 p=0.001 Withdrawals due to adverse events: Tx: 12.1 PBO: 2.9 p=0.002 EXTENSION PHASE: # withdrawn due to adverse events: T-T: 2 patients T-P: 4 patients	NA ARR: 17.3% NNH: 6 ARR: 9.2% NNH: 11	The study lacked a thorough description of randomization. Rates of adverse events were high in both study groups, but may be attributed to the nature of the disease of patients included in the trial. Treatment groups had significantly different HAART regimens at baseline. Efficacy endpoints for VAT and cholesterol remained significantly superior to placebo after controlling for increased NNRTI use in the treatment group. Antibodies developed in 50% of tesamorelin treated patients, the long-term implications of this are unknown. The primary endpoint is used as a surrogate marker of cardiovascular outcomes, for which there is limited evidence to support. Patients intolerant to tesamorelin likely discontinued treatment prior to re-randomization for the extension phase. This may contribute to the low withdrawal rate seen in the extension phase. LOCF used for subjects who didn't complete the study Initial phase, drop-out rates: 22.7% for tesamorelin 16.1% for placebo

Falutz, et al[9] RCT, DB, PC	1. Tesamorelin 2mg SQ daily 2. Placebo Extension Phase: 1) Tesamorelin 2mg SQ daily (T-T) 2) Placebo (T-P)	HIV+ patients stable on ART for ≥ 8 weeks with evidence of abdominal fat accumulation defined as a waist circumference of ≥ 95 cm and a waist-to-hip ratio of ≥ 0.94 for men and a waist circumference of ≥ 94 cm and a waist-to-hip ratio of ≥0.88 for women. Baseline characteristics similar between groups. Exclusions Criteria: Type 1 or 2 diabetes, serum creatinine >1.5, elevated liver enzymes, history of malignancy, untreated hypothyroidism or hypertension	N=404 Randomized 2:1, tesamorelin:PBO Tx: n=270 PBO: n=126 Extension Phase (randomized 1:1) T-T: n=92 T-P: n=85	RCT – 26 weeks Extension phase (6 months) – subjects who remained in the trial for the extension phase were re-randomized 3:1 to receive tesamorelin or placebo.	• **% Δ VAT** Tx: -10.9% PBO: -0.6% p<0.001 • **% Δ IGF-I** Tx:85.8 PBO:5.6 p<0.001 • **% Δ Total cholesterol** Tx: 2.1 PBO: 3.9 p=0.10 • **% Δ fasting glucose** Tx: 3.2 PBO: 2.7 p=0.15 EXTENSION PHASE • **% Δ VAT** T-T: 17.5% p<0.001 T-P: 1.3% p=0.432	NA	% patients experiencing any AE: Tx: 74.1 PBO:69.8 p=0.398 % patients experience treatment-related AE: Tx: 53 PBO: 37.3 p=0.005 % Withdrawals due to adverse events: Tx: 10 PBO: 8.7 p=0.855 EXTENSION PHASE: % patients experiencing any AE: T-T: 73.9% T-P:57.6% Withdrawals due to adverse events: T-T: 2.2% T-P: 4.7%	NA ARR: 15.7% NNH: 7 NA	Despite the reduction in VAT, glucose levels were not improved. The author suggests this is due to possible disruption of insulin functionality but this is counterbalanced by the improvement in VAT. There was no significant impact on triglyceride levels as seen in previous trials. This could be related to lower baseline TRG levels or variation in diets for patients treated at European centers. There is no evidence to show that improved body image distress correlates with improved adherence. The primary endpoint is used as a surrogate marker of cardiovascular outcomes, for which there is limited evidence to support. Adverse event rates were similar in the extension phase and in the primary phase. Patients intolerant to tesamorelin likely discontinued treatment prior to re-randomization for the extension phase. This may contribute to the low withdrawal rate seen in the extension phase. Initial phase, drop-out rates: 25% for tesamorelin 27% for placebo

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

Summary of Findings –

Tesamorelin was studied in two phase 3 trials that were identical in study design. Each randomized, placebo-controlled trial included patients with HIV who were stable on antiretroviral therapy for at least 8 weeks, and randomized them 3:1 to receive tesamorelin 2mg subcutaneously daily or placebo for 26 weeks. After 26 weeks, patients were re-randomized to tesamorelin or placebo for a 26 week extension phase. For both studies, the primary efficacy endpoint was the change in visceral adipose tissue (VAT) from baseline to week 26, measured by computerized tomographic (CT) scan.

A secondary endpoint was the impact on body image perception measured by a questionnaire in which subjects rated their belly size [from thinner (-100) to much bigger (+100)], belly image distress [extremely distressing (0) to extremely encouraging (100)], and belly profile by choosing from 6 silhouettes. Other secondary endpoints included changes in lipid levels and biochemical measures such as Insulin-like growth factor I (IGF-I) and blood glucose. The goal of the extension phase was to assess the long term safety of tesamorelin and evaluated effects on glucose, insulin, and body image.

Both studies saw a statistically significant change in VAT in patients treated with tesamorelin (-15.2% and -10.9%) compared to placebo (+5.0% and -0.6%, $p<0.001$ for both trials). Efficacy endpoints from the extension phases indicate that this decrease in VAT is not maintained after treatment discontinuation and these results were not seen in patients switched to placebo in the extension arm. Both studies also found no significant difference in the change in body mass index (BMI) after 26 weeks when comparing patients treated with tesamorelin versus placebo. In one study (2010), the BMI slightly increased in patients treated with tesamorelin (+0.6%).

The impact of tesamorelin on lipid levels slightly varied between the two studies. In the earlier study, there was a significant difference in the change in triglycerides when comparing tesamorelin to placebo (-7.5% vs +11.6%, $p<0.001$). Additionally, the change in the ratio of total cholesterol to HDL cholesterol was -4.7% in the tesamorelin group compared to +6.1 in the placebo group, $p<0.001$). In the second study, the change in triglycerides was not significant when compared to placebo (+2.8% vs +7.6%, $p=0.10$), and patients in the tesamorelin group actually saw a slight increase in triglyceride levels. There was also no difference in the change in ratio of total cholesterol to HDL cholesterol (+1.5% in the tesamorelin group vs +5.0% in the placebo group, $p=0.10$).

Despite a very small change in waist circumference in either study (-2.2cm and -2.6cm), as well as no difference in questionnaire scores for “belly size” after 26 weeks, there was a significant change in patient scores for “belly image distress.” Biochemical measures showed that patients treated with tesamorelin saw an increase in IGF-I (+81% and +85.8%) but had little impact on fasting glucose levels (+3.7% and +3.2%).

Overall, rates of adverse events and any serious adverse events were high, but similar between the two treatment groups, which may be due to the nature of the disease in this patient population. In the earlier study, 53.8% of patients treated with tesamorelin experienced treatment-related side effects compared to 36.5% treated with placebo, and 12.1% of tesamorelin-treated patients discontinued the study. The most common adverse

events were headache, arthralgias, injection-site bruising, diarrhea, peripheral edema, myalgia, and limb pain. These results were consistent with safety results seen in the second study, with the exception being that there was no significant difference in the percent of patients who discontinue the study due to adverse events (10% tesamorelin vs 8.7% placebo, p=0.855).

After 26 weeks of treatment, the mean HbA1c was higher among patients treated with tesamorelin compared to placebo; the mean treatment difference for patients receiving tesamorelin was +0.12% (p=0.0004) while the HbA1c of patients in the placebo group did not change from baseline. Patients in the tesamorelin group had an increased risk of developing diabetes compared to placebo [4.5% vs 1.3%, HR 3.3 (1.4,9.6)].

In the first extension phase, there were 154 patients who were treated with tesamorelin for the entire 52 weeks. Rates of adverse events were lower than those seen in the initial efficacy phase at the end of 26 weeks. Overall, 57.8% of patients experienced any adverse event, 14.3% experienced treatment-related adverse events, and 2.6% discontinued the study. These are similar to the results seen in the extension phase of the second study. In this study, 92 patients were treated with tesamorelin for the entire 52 weeks, and 73.9% experienced an adverse event, 37% experienced an adverse event related to the study treatment, but only 2.2% resulted in study discontinuation. These are slightly lower than the rates seen in the initial efficacy phase of the trial (2010).

DRUG SAFETY:

Contraindications[1,2]:

- patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, or pituitary tumor/surgery, head irradiation or head trauma
- active malignancy
- known hypersensitivity to tesamorelin and/or mannitol
- pregnancy

Warnings and precautions[1,2]:

Neoplasms: Patients with a history of non-malignant neoplasms should only begin tesamorelin treatment after careful evaluation of the potential benefit of treatment. The decision to start treatment with tesamorelin should be considered carefully based on the increased background risk of malignancies in HIV-positive patients.

Elevated IGF-1: The impact of elevated IGF-1 levels on the development of malignancies is unknown. Careful consideration should be given to discontinuing tesamorelin in patients with persistent elevations in IGF-1 levels.

Fluid retention: Fluid retention may result in a variety of adverse reactions which are either transient or will resolve with discontinuation of treatment.

Glucose intolerance: Tesamorelin treatment may result in glucose intolerance. An increased risk of developing diabetes with tesamorelin relative to placebo was observed in clinical trials [HR 3.3 (1.4,9.6)]. Therefore, glucose status should be carefully evaluated prior to initiating tesamorelin treatment. Patients should be monitored periodically for changes in glucose metabolism to diagnose those who develop impaired glucose tolerance or diabetes.

Hypersensitivity reactions: Hypersensitivity 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 should be discontinued immediately.

Injection site reactions: Reactions include injection site erythema, pruritus, pain, irritation, and bruising. In order to the incidence of injection site reactions, it is recommended to rotate the site of injection to different areas of the abdomen.

Acute critical illness: Increased mortality was see 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. Tesamorelin has not been studied in patients with acute critical illness.

Tolerability: During the initial treatment phase of clinical trials, discontinuations as a result of adverse reactions occurred in 9.6% of patients receiving tesamorelin and 6.8% of patients receiving placebo. The most common reasons for discontinuation of tesamorelin treatment were adverse reactions due to the effects of growth hormone (4.2%) and local injection site reactions (4.6%). Dueing the 26-week extension phases, discontinuations as a result of adverse events occurred in 2.4% of patients in the T-T group and 5.2% of patients in the T-P group.

Pregnancy/Lactation rating: Pregnancy category X. Visceral adipose tissue increases during pregnancy and modifying this offers no known benefit and may result in fetal harm. Administration to rats during organogenesis and lactation produced hydrocephaly in offspring at a dose 2-4x higher than the clinical dose.

Unanswered safety questions:
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. Additionally, since tesamorelin increases IGF-1, patients with diabetes who are receiving ongoing treatment with tesamorelin should be monitored at regular intervals for potential development of worsening of retinopathy.

Dose Index (efficacy/toxic): Not applicable

Look-alike / Sound-alike (LA/SA) Error Risk Potential
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for [generic]	temisirolimus				
LA/SA for [brand]					

Incidence of patients (%) with adverse drug reactions		
Adverse Events (1) **(MedDRA System Organ Class and Preferred Term)**	**Tesamorelin**	**Control**
Number of Patients	543	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
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
Gastrointestinal disorders		

Nausea	4.4	3.8
Vomiting	2.6	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
Investigations		
Blood creatine phosphokinase increased	1.5	0.4

DOSE & AVAILABILITY: [1,2]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
1mg	vial	SQ	2mg once daily	N/A	N/A	Not studied	Not studied	None

PHARMACOKINETICS: [1,2]

Parameter	Result
Bioavailability	4%
Cmax	2822.3 pg/mL
Protein Binding	Not reported
Elimination	Not reported
Half-Life	38 minutes in HIV-infected patients
Metabolism	Not studied in humans

ALLERGIES/INTERACTIONS:[1,2]

Drug-Drug:

Possible interactions with CYP P450 metabolized drugs. Monitor during concurrent use with tesamorelin.

Patients receiving glucocorticoid replacement for hypoadrenalism may require an increase in maintenance or stress doses following initiation of tesamorelin.

Food-Drug: None

Allergy/Cross Reactive Substances: None

Suggested PA

Tesamorelin (Egrifta)

Goal(s):

- Cover for only OHP covered diagnoses.
- Restrict to indications supported by medical literature.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis a reduction of excess abdominal fat in HIV-infected patients with lipodystrophy?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness).
3. Is the diagnosis an OHP covered diagnosis?	Yes: Approve for 6 months	No: Pass to RPH; Deny, (Not covered by the OHP).

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