CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

Tesamorelin
(Egrifta — Theratechnologies Inc.)
Indication: HIV-associated lipohypertrophy

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tesamorelin not be reimbursed for the treatment of excess visceral adipose tissue (VAT) in treatment-experienced adult HIV-infected patients with lipodystrophy.

Reasons for the Recommendation:

1. Three randomized placebo-controlled clinical trials suggested that tesamorelin can reduce the amount of VAT in treatment-experienced adult HIV-infected patients with lipodystrophy. However, the change in VAT is a surrogate outcome and there is inconsistent evidence that the reduction in VAT observed in tesamorelin-treated patients improves patient-reported outcomes such as body image. In addition, there is no evidence that tesamorelin treatment reduces the risk of cardiovascular events.
2. There is insufficient evidence regarding the long-term safety of tesamorelin therapy, which is of concern because tesamorelin may be used for extended periods due to the re-accumulation of VAT that occurs upon cessation of tesamorelin therapy.

Of Note:
1. The Committee noted that even though tesamorelin is the only pharmacological therapy approved for patients who fail to reduce excess VAT using diet, the evidence did not allow for an adequate assessment of the clinical benefits of the effects of tesamorelin in such patients.

Background:
Tesamorelin has a Health Canada indication for the treatment of excess VAT, as assessed by waist circumference ≥ 95 cm for males and ≥ 94 cm for females, and confirmed by a VAT level > 130 cm^2 by computed tomography (CT) scan, in treatment-experienced adult HIV-infected patients with lipodystrophy.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) and pivotal studies of tesamorelin; a critique of the manufacturer's pharmacoeconomic evaluation; and patient group–

submitted information about outcomes and issues important to lipodystrophy patients with excess VAT.

Patient Input

One patient group, the Canadian Treatment Action Council (CTAC), responded to the CDR call for patient input. Information was gathered via an online survey following a national patient input consultation webinar. The following issues were raised in the patient input received by CADTH:

- VAT is difficult to reduce with diet and exercise.
- Excess VAT is associated with self-esteem issues, negative body image, reduced quality of life, and problems with socializing.
- Tesamorelin is the only pharmacological treatment available for excess VAT, and while its side effects were described as manageable, an important caveat noted by patients was that tesamorelin needs to be taken chronically for life; otherwise, there is a possibility of reversal of effects.
- Patients emphasized their high hopes for this treatment in helping to reduce or eliminate self-esteem problems associated with a negative body image.
- The handful of patients who reported on their experience with tesamorelin said the therapy had been effective.

Clinical Trials

Three RCTs (LIPO-010 [N = 412], CTR-1011 [N = 404], and Stanley et al. 2014 [N= 54]), each of which compared tesamorelin 2 mg/day (subcutaneous injection) with placebo, were included in the systematic review. LIPO-010 and CTR-1011 were multi-centre, double-blind, placebo-controlled, phase 3 RCTs. Each study comprised a 26-week double-blind main phase, followed by a 26-week extension phase (the extension phase of CTR-1011 was denoted as CTR-1012). The study by Stanley et al. 2014 was a single-centre, double-blind, placebo-controlled RCT that enrolled participants exclusively from the US. All trials enrolled HIV-positive adults aged 18 to 65 years who were on a stable antiretroviral therapy (ART) regimen who had abdominal fat accumulation defined by: waist circumference ≥ 95 cm and waist-to-hip ratio ≥ 0.94 for males, and waist circumference ≥ 94 cm and waist-to-hip ratio ≥ 0.88 for females.

Outcomes

The following outcomes were defined a priori in the CDR systematic review protocol:

- VAT (as measured by CT scan)
- Waist circumference
- Body image
- Quality of life (QoL) and health-related QoL
- Mortality, adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and notable harms (injection-site reactions, myalgia, arthralgia, fluid retention or edema, diabetes, and malignancies).

The primary efficacy outcome for LIPO-010 and CTR-1011 was the per cent change in VAT at week 26. In Stanley et al. 2014, the co-primary efficacy outcomes were changes in VAT assessed by CT scan and liver fat (not relevant for this review).

Efficacy

Across all three included studies, tesamorelin was associated with a statistically significantly greater reduction in VAT versus placebo: the least squares (LS) mean differences (95% confidence interval [CI]) for tesamorelin versus placebo were –19.6% (–23.7% to –15.3%) in LIPO-010 at week 26, and –11.7% (–16.2% to –7.1%) in CTR-1011 week 26, and −16.6% (−30.6% to −2.6%) in Stanley et al. 2014 at six months. In LIPO-010 and CTR-1011, tesamorelin was associated with a statistically significantly greater reduction in waist circumference at 26 weeks versus placebo, with absolute differences (95% CI) of –1.8 cm (–2.8 cm to –0.9 cm) and –1.3 cm (–2.4 cm to -0.2 cm), respectively. While these differences exceeded the pre-determined threshold for clinical significance of 1 cm, this threshold was not rigorously derived. Accordingly, the clinical significance of these results is uncertain. In the same two trials, at week 26, there were no statistically significant differences between treatment groups with respect to change in belly size evaluation, while the effects of tesamorelin versus placebo on change in belly appearance distress and patient-reported belly profile ratings were inconsistent. The scales used to measure changes in belly size and distress have not been thoroughly evaluated and the clinical significance of the observed changes is uncertain. There were no statistically significant differences between tesamorelin and placebo with respect to changes to the overall (item-wise) QoL score at week 26.

In the extension phase, continued treatment with tesamorelin (T-T group) was associated with a statistically significantly greater reduction in VAT versus discontinuing treatment with tesamorelin (T-P group) from weeks 26 to 52: LS mean differences (95% CI) were –20.4% (–29.8 to –11.0) and –25.8% (–40.7% to –10.9%) in LIPO-010 and CTR-1012, respectively. For both trials, however, participants in the T-P group experienced increases in VAT by as much as 24.9% over the same time period. Furthermore, from weeks 26 to 52, participants in the T-T group experienced statistically significantly greater improvements in belly appearance distress and patient-reported belly profile versus those in the T-P group, although there were no statistically significant differences between treatment groups with respect to changes in belly size evaluation.

Harms

Across all three studies, at least 70% of study participants in each trial experienced a TEAE at week 26. A greater proportion of participants in Stanley et al. 2014 experienced an AE (tesamorelin: 89.3%; placebo: 95.5%) than those in the main phase of LIPO-010, followed by those in CTR-1011. Approximately 5% more participants receiving tesamorelin (LIPO-010: 82.8%; CTR-1011: 74.1%) experienced an AE than those on placebo (LIPO-010: 75.9%; CTR-1011: 69.8%). There were no deaths in LIPO-010 and Stanley et al. 2014, whereas two participants died in CTR-1011 — one in each treatment group.

Across all three studies, at week 26, a greater percentage of participants receiving tesamorelin reported an injection site–related AE, myalgia, or fluid retention or edema than those in the placebo group. In LIPO-010, one participant (0.4%) receiving tesamorelin (versus none receiving placebo) developed diabetes mellitus (recorded as a TEAE) at week 26. In LIPO-010, a greater percentage of participants receiving tesamorelin versus placebo (2.9% versus 1.5%) developed a malignancy, whereas a smaller percentage of participants receiving tesamorelin in CTR-1011 versus those receiving placebo (0.4% versus 3.2%) developed a malignancy.

In the LIPO-010 extension phase, AEs were observed in 57.8%, 74.7%, and 73.9% of participants in the T-T, P-T, and T-P groups, respectively; the corresponding percentages in CTR-1012 were 73.9%, 57.6%, and 76.7%. Two participants died in the extension phase of LIPO-010 — one individual in the T-T group, and the other in the P-T group.

Cost and Cost-Effectiveness

The submitted price of tesamorelin is $3,085 per box of 60 × 1 mg vials (30-day supply), or $51.46 per 1 mg vial. The recommended dose is 2 mg (two 1 mg vials) injected subcutaneously once daily. The annual cost of treatment is $37,534 per patient.

The manufacturer submitted a cost-utility analysis comparing tesamorelin with standard of care (lifestyle modifications, nutrition, and physical activity) in a cohort of patients with HIV-associated lipohypertrophy. The time horizon was patient lifetime (30 years) and the model considered a Canadian public payer perspective. Patients entered the model being treated either by standard of care or tesamorelin. Patients were assumed to continue treatment for the full model time horizon. Patients could experience a cascade of clinical events: 1) complications or disease states associated with HIV-associated lipohypertrophy, or 2) consequences of suboptimal adherence to HIV treatment that is attributable to lipohypertrophy. All baseline risks of events, their relative risks of occurrence, and their associated costs and utility score were obtained from observational literature. Proportions of responders and non-responders to treatment were taken from the clinical trials assessing tesamorelin, with response defined as a ≥ 8% decrease in VAT. It was assumed that 50% of responders had a "complete" response, and the remaining 50% a "partial" response. Complete responders were assumed to revert to a risk of clinical events as per the general population, while it was assumed that partial responders would have a risk between that of complete responders and that of non-responders. A similar approach was taken for HIV treatment adherence, where responders and partial responders would have complete adherence. Discontinuation of tesamorelin due to AEs and mortality were not modelled. Standard of care was assumed to be associated with no cost.

CDR identified the following key limitations with the manufacturer's economic submission:

- Lack of appropriate evidence linking the surrogate outcome (reduction in VAT) to long-term clinical events related to lipohypertrophy and to non-adherence to HIV medication. This is a major limitation, considering that the predicted clinical benefits associated with tesamorelin are based on the premise of a direct association between VAT and events related to lipohypertrophy and medical adherence. VAT has not been validated as a surrogate for any of the clinical events modelled.
- Uncertain assumption of continued use of treatment and sustained treatment efficacy over a lifetime time horizon.
- AEs from the drug treatment were not included in the analysis, which favours tesamorelin.

Considering the identified limitations, the most plausible reference case for CDR was to assume no difference in future clinical events mediated through lipohypertrophy or non-adherence to HIV treatment between tesamorelin and standard of care, resulting in tesamorelin being more expensive ($611,657 over 30 years; $37,534 over one year) and equally effective compared with standard of care.

Research Gaps:
The Committee proposed that future research should be carried out to determine the long-term safety of tesamorelin. Future research should also be carried out regarding the link between the hypothetical cardiovascular benefits of reducing VAT.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

July 20, 2016 Meeting

Regrets:

None

Conflicts of Interest:

None

About This Document:
CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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