CADTH CANADIAN DRUG EXPERT COMMITTEE
CDEC FINAL RECOMMENDATION

TALIGLUCERASE ALFA
(Elelyso — Pfizer Canada Inc.)
Indication: Gaucher Disease

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that taliglucerase alfa not be listed for long-term enzyme replacement therapy (ERT) for adults and children with type 1 Gaucher disease (GD) or for hematological manifestations in pediatric patients with type 3 GD.

Reasons for the Recommendation:

1. Although the four included studies (001 [N = 33], 002 [N = 33], 004 [N = 59], and 005 [N = 11]) suggested that treatment with taliglucerase alfa is associated with improvements from baseline in hematological parameters, spleen volume, and liver volume, these studies are limited by the open-label administration of the study drug, lack of a comparator group, and relatively short duration of follow-up. Given these limitations, CDEC concluded that there is significant uncertainty regarding the clinical benefit of taliglucerase alfa for the treatment of GD.
2. In the absence of direct comparisons, CDEC considered the indirect comparison submitted by the manufacturer. However, there were several serious limitations of the indirect comparison, which was a naive side-by-side comparison that did not report formal statistics or estimates of relative effects.
3. Overall, CDEC concluded that there is insufficient evidence to evaluate the comparative clinical benefit of taliglucerase alfa compared with other ERTs that are currently available in Canada for the treatment of GD (i.e., velaglucerase alfa and imiglucerase).

Of Note:

- There are currently two other ERTs available in Canada for the treatment of GD; therefore, taliglucerase alfa does not address an immediate unmet clinical need for these patients.
- There is insufficient evidence to evaluate the effect of taliglucerase alfa on the prevention of bone crises, a key end point identified by the patient group.

Background:
Taliglucerase alfa is a recombinant form of human glucocerebrosidase, which catalyzes the degradation of the glycolipid glucocerebrosides and reduces its accumulation in organs and tissues. Taliglucerase alfa replaces the defective enzyme in GD, principally in macrophages. Taliglucerase alfa is indicated for long-term ERT for adults and children (two to 17 years old) with a confirmed diagnosis of type 1 GD and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD.

Taliglucerase alfa is supplied as a lyophilized, sterile powder in a single-use vial designed to deliver 200 units (U) of taliglucerase alfa for intravenous infusion upon reconstitution. Taliglucerase alfa is administered intravenously over one to two hours every two weeks at initial doses ranging from 30 U/kg to 60 U/kg.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials and pivotal studies of taliglucerase alfa, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with GD and their caregivers.

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- GD is associated with a wide range of disease severity among patients, with various physical, emotional, social, and financial challenges. While some patients have mild symptoms that do not require treatment, those with more severe disease experience bone pain, degeneration of joints, spontaneous fractures, bone necrosis, and pronounced liver and spleen enlargement, resulting in abdominal discomfort and distension. Some patients with GD commonly experience bone crises, which are associated with excruciating pain and often require hospitalization.
- The psychological impact of GD can be profound for both patients and their caregivers. Decreased stamina, frequent pain, and immobility can all have a major impact on the careers and social lives of patients, caregivers, and families. Children and adolescents are particularly conscious of their body image, and teasing related to their appearance can have a serious impact on their self-esteem.
- Patient groups indicated that additional treatment options for GD would be beneficial for those experiencing adverse effects from their current therapy and would help ensure that alternative ERTs are available in the event of drug shortages.

Clinical Trials
The CDR systematic review included the following four studies:

- Studies 001 and 005 were multi-centre, dose-blind, uncontrolled randomized trials comparing two doses of taliglucerase alfa (30 U/kg and 60 U/kg) in previously untreated patients. Study 001 (N = 33) was nine months in duration and enrolled adult type 1 GD patients. Study 005 (N = 11) was 12 months in duration and enrolled pediatric type 1 and 3 GD patients. Patients received taliglucerase alfa every two weeks.

- Study 002 was an open-label study conducted to assess the stability of switching clinically stable adult (n = 28) and pediatric (n = 5) type 1 GD patients from imiglucerase to taliglucerase alfa. Patients received taliglucerase alfa every two weeks at a dose equivalent to their stable imiglucerase dose.
- Study 004 (N = 59) was an open-label study conducted to evaluate the safety of taliglucerase alfa in adult GD patients who were previously treated with imiglucerase. The study duration was up to 33 months, which included a mandatory phase of nine months and an additional phase of 24 months or until marketing approval was obtained. Patients received taliglucerase alfa every two weeks at a dose equal to the patient's previous imiglucerase dose.

The CDR review also summarized the findings of study 003, an extension phase of studies 001 and 002.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol:

- Spleen and liver volume — organ volumes were measured by magnetic resonance imaging using a standardized protocol for capturing images. Images were read by two independent radiologists at a central reading centre. Normal spleen and liver volumes were estimated as 2 mL/kg and 25 mL/kg of body weight, respectively.
- Change from baseline in hematologic end points: hemoglobin levels and platelet counts.
- Change from baseline biomarkers: chitotriosidase activity and chemokine (C-C motif) ligand 18 (CCL18) levels.
- Bone disease was evaluated using the following:
  - Dual-energy X-ray absorptiometry (DEXA) — used to measure bone mineral density (BMD). T score compares DEXA results to the ideal BMD of a healthy 30-year-old adult and z score compares the DEXA results to age- and sex-matched controls.
  - Quantitative chemical shift imaging (QCSI) — used to quantify bone marrow response (fat fraction content) to ERT in GD.
- Growth evaluation in children — height and weight were measured.
- Child Health Questionnaire Parent Form 28 (CHQ-PF28) — a questionnaire used to assess the quality of life for children for the last four weeks on dimensions such as family cohesion, global health, physical functioning, and self-esteem. Items are scored and summed to produce scales (standardized scores) that range from 0 to 100; 0 is the worst possible and 100 the best possible health state.
- Total adverse events, serious adverse events, withdrawals due to adverse events, and notable harms.

The primary objectives of the studies were as follows:

- Study 001: to evaluate the efficacy of taliglucerase alfa as reflected by the percentage reduction from baseline of spleen volume after nine months
- Study 002: to assess the clinical stability as measured with platelet counts, hemoglobin levels, and spleen and liver volumes after nine months
- Study 004: to evaluate the safety of switching from imiglucerase to taliglucerase alfa
- Study 005: to evaluate the efficacy of taliglucerase alfa as measured by the median percentage change in hemoglobin levels from baseline after 12 months.

Efficacy

- In study 001, hemoglobin levels were statistically significantly improved from baseline for both the 30 U/kg ($P = 0.0010$) and 60 U/kg ($P < 0.0001$) taliglucerase alfa groups, with no statistically significant difference between the two groups ($P = 0.719$). The mean changes from baseline (standard deviation [SD]) were:
  - Study 001: 1.6 g/dL (1.4) for 30 U/kg and 2.2 g/dL (1.4) for 60 U/kg
  - Study 002: –0.2 g/dL (0.7) for adult and 0.4 g/dL (1.4) for pediatric patients
  - Study 004: 0.5 g/dL (1.2)
  - Study 005: 1.4 g/dL (1.3) for 30 U/kg and 1.6 g/dL (0.7) for 60 U/kg.
- Platelet counts were statistically significantly improved from baseline for the 60 U/kg group in study 001 ($P = 0.0031$), but not for the 30 U/kg group ($P = 0.0460$; alpha = 0.025). There was a statistically significant difference between the two taliglucerase alfa dosage groups ($P < 0.042$). The mean changes from baseline (SD) were:
  - Study 001: 11,427/mm^3 (20,214) for 30 U/kg and 41,494/mm^3 (47,063) for 60 U/kg
  - Study 002: –2,527/mm^3 (29,871) for adult and 12,813/mm^3 (43,756) for pediatric patients
  - Study 004: 29,205/mm^3 (30,266)
  - Study 005: 45,500/mm^3 (52,884) for 30 U/kg and 72,600/mm^3 (59,197) for 60 U/kg.
- In study 001, spleen volumes were statistically improved from baseline for both the 30 U/kg and 60 U/kg groups (both $P < 0.0001$), with no statistically significant difference between the two groups ($P = 0.060$). The mean percentage changes from baseline (SD) were:
  - Study 001: –26.91% (7.79) for 30 U/kg and –38.01% (9.38) for 60 U/kg
  - Study 002: –7.6% (13.3) for adult and –6.6% (15.6) for pediatric patients
  - Study 005: –28.6% (21.5) for 30 U/kg and –41.1% (13.8) for 60 U/kg.
- In study 001, liver volumes were statistically improved from baseline for both the 30 U/kg ($P = 0.0041$) and 60 U/kg ($P < 0.0001$) groups, with no statistically significant difference between the two groups ($P = 0.349$). The mean percentage changes from baseline (SD) were:
  - Study 001: –10.48% (11.27) for 30 U/kg and –11.11% (6.68) for 60 U/kg
  - Study 002: –3.5% (8.1) for adult and 2.4% (6.8) for pediatric patients
  - Study 005: –6.3% (8.5) for 30 U/kg and –14.0% (9.0) for 60 U/kg.
- In study 001, chitotriosidase levels were statistically improved from baseline for both the 30 U/kg ($P < 0.0001$) and 60 U/kg ($P = 0.0016$) groups. The mean changes from baseline (SD) were:
  - Study 001: –13,264 nmol/mL/h (8378.2) for 30 U/kg and –12,165 nmol/mL/h (12,064) for 60 U/kg
  - Study 002: –1,206 nmol/mL/h (1685) for adult and –1,877 nmol/mL/h (2,425) for pediatric patients
  - Study 005: –13,210 nmol/mL/h (9811.6) for 30 U/kg and –20,528 nmol/mL/h (8,715.4) for 60 U/kg
- Mean changes from baseline in CCL18 levels (SD) were:
  - Study 002: –6.6% (19.3) for adult and –4.4% (37.3) for pediatric patients
  - Study 005: –50.6% (19.4) for 30 U/kg and –52.6% (22.5) for 60 U/kg.
- In study 005, mean changes in height and weight (SD) were:
  - Height: 4.2% (2.2) for 30 U/kg and 7.6% (2.1) for 60 U/kg
  - Weight: 9.6% (7.0) for 30 U/kg and 14.7% (5.7) for 60 U/kg
  - Bone age by X-ray: 1.9 years (1.4) for 30 U/kg and 1.4 years (0.3) for 60 U/kg.

- Bone disease was assessed by DEXA in studies 001 and 005, but sample sizes were small and no statistical inferences were made. In study 001, changes in QCSI scores at nine months were 0.0700 for 30 U/kg and 0.1225 for 60 U/kg. In both studies, changes in z scores, t scores, and BMD from baseline were less than 0.7 points for all bone sites.
- Quality of life was assessed with CHQ-PF28 in Study 005. General health numerically improved from baseline for both treatment groups after 12 months, but sample sizes were small and no statistical inferences were made.

Harms (Safety and Tolerability)

- The proportions of patients who experienced at least one serious adverse event were:
  - Study 001: 0% for both groups
  - Study 002: 11.5% in adult patients and 0% in pediatric patients
  - Study 004: 3.4% of patients included in the safety set
  - Study 005: 0% with 30 U/kg and 20.0% with 60 U/kg.
- The proportions of patients who experienced at least one adverse event were:
  - Study 001: 75.0% with 30 U/kg and 68.8% with 60 U/kg
  - Study 002: 96.2% in adult patients and 80.0% in pediatric patients
  - Study 004: 91.4% of patients included in the safety set
  - Study 005: 83.3% with 30 U/kg and 100.0% with 60 U/kg.
- The most commonly reported adverse events were headache (total occurrence of 19.7%), arthralgia (16.7%), upper respiratory tract infection (14.4%), and nasopharyngitis (12.9%). No increased occurrence could be associated with a specific dosing regimen.
- The proportions of patients who withdrew as a result of adverse events were:
  - Study 001: 6.3% for each group
  - Study 002: 0%
  - Study 004: 3.4% of patients included in the safety set
  - Study 005: 0%.
- Infusion-related and hypersensitivity reactions occurred in 5.3% and 4.5% of all patients, respectively. There were no cases of anaphylaxis reported in any of the studies.
- A positive anti–taliglucerase alfa antibody test was reported for 22.7% of all patients.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-consequence analysis (CCA) over a one-year time horizon from the perspective of the publicly funded health care system in Canada, comparing taliglucerase alfa with other available ERTs (imiglucerase and velaglucerase alfa) and no ERT in patients with type 1 GD and type 3 GD. The CCA considered the following costs: drug acquisition, adverse events, and surgery. Although not specified in the manufacturer's pharmacoeconomic submission, the manufacturer's cover letter indicated a listing request for reimbursement by provinces that already list ERTs. Administration costs were assumed to be equal among all ERTs; the manufacturer indicated it had set up a patient support program that includes provision of administration. Comparative effectiveness and safety comparisons were based on two systematic reviews, while data from clinical registries were used to inform efficacy for no ERT. Data for adverse events were derived from the product monographs and from the manufacturer's data for taliglucerase alfa. The manufacturer indicated that the total costs per year associated with treatment with taliglucerase alfa ($337,725) were lower than the costs associated with velaglucerase alfa ($510,627) and imiglucerase ($640,178), but higher than for no ERT ($1,578).

CDR identified the following limitations with the manufacturer's pharmacoeconomic submission:

- Lack of comparative information for taliglucerase alfa versus the two other ERTs available for treatment of GD
- Uncertainty regarding costing of comparative harms data
- Uncertainty regarding the reimbursement criteria, and their applicability to all participating public drug plans
- The use of a short time horizon for a condition with long-term impacts
- Data for the type 3 GD and pediatric patients were not included in the comparative analysis for the economic submission
- Two published cost-effectiveness analyses of ERT in GD were identified, but neither was used to inform a cost-effectiveness analysis for this submission.

As there is no comparative clinical information available for taliglucerase alfa relative to other available ERTs, whether taliglucerase alfa is clinically similar to other ERTs could not be assessed; additionally, given the submitted economic evaluation, the cost-effectiveness of taliglucerase alfa could not be assessed for jurisdictions that do not reimburse ERTs. At the submitted price of $3.24 per unit, taliglucerase alfa is less costly than the other ERTs ($4.89 to $6.15 per unit).

Other Discussion Points:

CDEC noted the following:

- Patient group input noted that bone crises were among the most important concerns for GD; however, there were insufficient data from the included studies to evaluate the efficacy of taliglucerase alfa for the prevention of these events.
- In the absence of direct comparisons, CDR summarized and appraised three systematic reviews comparing taliglucerase alfa with other treatments for GD. Two of the systematic reviews were submitted by the manufacturer to provide a naive side-by-side comparison of the available ERTs for the treatment of GD, both of which had numerous methodological limitations. The three systematic reviews concluded that no difference for efficacy and safety could be observed between the different available ERTs; however, the quality of the evidence is limited and there remains considerable uncertainty regarding the comparative efficacy and safety of taliglucerase alfa against the other ERTs.
- Taliglucerase alfa was administered in an open-label manner in the included studies, which could influence the results of the subjective outcomes (e.g., CHQ-PF28).
- None of the included trials used an intention-to-treat analysis, which could bias the results. This is particularly relevant for study 004, in which 29% of patients discontinued taliglucerase alfa before the nine-month end point of the study.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no studies directly comparing taliglucerase alfa with other ERTs available in Canada for the treatment of GD.
- The included trials enrolled few pediatric patients (n = 16).
- Only two patients with type 3 GD were enrolled in the trials, and these two patients did not demonstrate a response to the treatment (i.e., 30 U/kg taliglucerase alfa biweekly).

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.

Regrets:
July 15, 2015: None
October 21, 2015: None

Conflicts of Interest:
July 15, 2015: None
October 21, 2015: None

About this Document:
CDEC provides formulary listing 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.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.