CEDAC FINAL RECOMMENDATION

VELAGLUCERASE ALFA
(VPRIV – Shire Human Genetic Therapies Inc.)
Indication: Gaucher Disease

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that velaglucerase alfa be listed for patients with type 1 Gaucher Disease (GD1) in jurisdictions that provide funding for imiglucerase, when it is cost saving to do so.

Reasons for the Recommendation:
1. In one small (N = 35) double-blind randomized controlled trial (RCT) of patients with GD1, velaglucerase alfa was reported to be non-inferior to imiglucerase, based on improvements in mean hemoglobin concentration.
2. Velaglucerase alfa is less costly compared with imiglucerase (subject to dose and patient weight).

Of Note:
1. On a per unit (U) basis, velaglucerase alfa ($4.89/U) is less costly than imiglucerase ($6.15/U). However, given the potential for drug wastage and the availability of 200 U and 400 U vials of imiglucerase (compared with only 400 U vials of velaglucerase alfa), for some dose and weight combinations, imiglucerase may be less costly (e.g., pediatric patients who weigh less than 10 kg and who require doses of 45 U/kg to 60 U/kg).
2. The Committee noted that velaglucerase alfa is not an alternative for those patients in whom imiglucerase does not provide sufficient benefit.

Background:
Velaglucerase alfa has a Health Canada indication as a long-term enzyme replacement therapy for pediatric and adult patients with GD1. It is available as a sterile lyophilized powder in single-use vials of 400 U per vial. The Health Canada-approved dose is 60 U/kg administered every other week as a 60-minute intravenous (IV) infusion.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of velaglucerase alfa, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included one double-blind RCT of patients with GD1. Study HGT-GCB-039 (hereafter referred to as study 039) was a nine-month multinational study designed to test the non-inferiority of velaglucerase alfa 60 U/kg IV every two weeks, compared with imiglucerase 60 U/kg IV every two weeks. Thirty-five patients were randomized (1:1) to either treatment. Patients in the trial were predominantly treatment naive and mostly had mild anemia and either thrombocytopenia or organomegaly. Six per cent of patients in each treatment group withdrew from the trial during treatment.

Limitations of the trial include the small sample size, unequal distribution of children under the age of seven years between treatment groups, and the lack of justification for the non-inferiority margin employed. In addition, patients in the trial were not required to have symptomatic disease, and thus trial results may not reflect the response to velaglucerase alfa for symptomatic patients.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: hematological parameters, including hemoglobin concentration and platelet count; liver and spleen size changes; quality of life; serious adverse events; and adverse events. The primary outcome in the trial was the mean absolute change in hemoglobin concentration from baseline to week 41. The trial was designed to accept the non-inferiority of velaglucerase alfa compared with imiglucerase for the primary outcome if the lower limit of the one-sided 97.5% confidence interval (CI) for the absolute treatment difference was above –1g/dL.

Outcomes of importance, identified by patient groups, were noticeably missing from the trial; these include bone complications, pain, and fatigue.

Results

Efficacy or Effectiveness
- Mean hemoglobin concentrations improved from baseline to week 41 for both treatments in the intention-to-treat population, from 11.5 g/dL to 13.1 g/dL in the velaglucerase alfa group, and from 10.5 g/dL to 11.9 g/dL in the imiglucerase group. Velaglucerase alfa was reported to be non-inferior to imiglucerase (non-inferiority margin of –1 g/dL) based on the between-treatment difference; mean difference (MD): 0.136 g/dL, 95% CI: –0.596 to 0.867. Non-inferiority of velaglucerase was also demonstrated for the per-protocol population.

- Platelet counts increased by 77.2% and 110.7% from baseline to week 41 in the velaglucerase alfa and imiglucerase treatment groups, respectively; between-treatment differences were not statistically significant.
- Both treatments produced clinically relevant reductions in body-weight normalized liver and spleen volumes from baseline to week 41 (–1.1% and –1.3% for imiglucerase and velaglucerase respectively for the liver, and –2.5% and –1.3% for imiglucerase and velaglucerase respectively for the spleen); between-treatment differences were not statistically significant.
- There were no significant improvements in quality of life in either the velaglucerase alfa or imiglucerase treatment groups as measured by the SF-36 health survey domain scores, or the physical or mental component summary scores of the SF-36 health survey.
- The study was of too short a duration to provide meaningful data regarding reduction of bone complications, which, according to the information submitted by patient groups, has a large negative impact on patients' quality of life.

Harms (Safety and Tolerability)

- Patients experiencing serious adverse events were more numerous in the velaglucerase alfa treatment group compared with imiglucerase; three patients compared with none, respectively. Serious adverse events observed with velaglucerase alfa included allergic dermatitis, life-threatening convulsions, and thrombocytopenia.
- No patients in either treatment group withdrew from the trial because of adverse events.
- The most common adverse events observed in both treatment groups included arthralgia, pyrexia, influenza, nasopharyngitis, and headache.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing velaglucerase alfa to imiglucerase in individuals with GD1. The clinical evidence to support the use of a cost-minimization analysis was based on study 039, which provided evidence to support the non-inferiority of velaglucerase compared with imiglucerase regarding change in hemoglobin concentration.

The average annual cost of velaglucerase alfa ranges from $50,830 to $609,960, depending on the weight of the individual (range: 20 kg to 80 kg) and dose of treatment (range: 30 U/kg to 60 U/kg). Compared with imiglucerase, the only other enzyme replacement therapy available for GD1 in Canada, velaglucerase alfa, could represent an increase of $5,720 to a cost saving of $157,560 per patient per year, depending on the dose of GD1 treatments and the amount of wastage.

Patient Input Information:

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

- Bone complications of GD1 were noted to have the greatest negative impact on quality of life. In addition, physical symptoms such as pain and fatigue cause significant distress to patients and impact their ability to work and participate in leisure activities.
- A recent shortage of imiglucerase due to shutdown of a manufacturing plant in 2009 resulted in interruptions in treatment and caused significant distress to patients. Patients

expect that velaglucerase alfa would serve as an effective alternative to imiglucerase, which would provide some insurance against future possible supply disruptions.

Other Discussion Points:

- While velaglucerase alfa appears to improve hematological parameters and hepatosplenomegaly, these effects of GD1 do not contribute to significant morbidity unless anemia is severe and/or organomegaly is marked. The effect of velaglucerase on life expectancy is unknown.

CEDAC Members Participating:
Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:
Dr. Anne Holbrook (Vice-Chair)

Conflicts of Interest:
None

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation 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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