



## CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

### GLYCEROL PHENYLBUTYRATE (Ravicti — Horizon Therapeutics Canada) Indication: Urea Cycle Disorders

#### **Recommendation:**

The CADTH Canadian Drug Expert Committee (CDEC) recommends that glycerol phenylbutyrate (GPB) be reimbursed for the use as a nitrogen-binding drug for chronic management of adult and pediatric patients  $\geq 2$  years of age with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone, if the following conditions are met:

#### **Conditions:**

1. Drug plan cost not to exceed the drug plan cost of sodium phenylbutyrate (NaPB).
2. Patient to be managed with input from a physician with expertise in the treatment of patients with UCD.

#### **Reasons for the Recommendation:**

1. One phase III, double-blind, crossover, active controlled, randomized controlled trial (RCT) demonstrates that GPB is noninferior to NaPB in terms of effect on ammonia levels.
2. At the manufacturer-submitted price, the price of GPB is 46% higher than the price of NaPB (Pheburane).

#### **Of Note:**

- The clinical trial reviewed included only patients with three subtypes of UCD involving deficiencies of carbamoyl phosphate synthetase 1, ornithine transcarbamylase, or argininosuccinate synthetase. However, CDEC recognized the population affected by UCD is small; therefore, it is challenging to enrol sufficient numbers of patients in the clinical trials and reimbursement should not be restricted to these three subtypes.
- CDEC discussed that for patients receiving drug through a g-tube, GPB administration may be more practical than NaPB, but no data were available to evaluate use in this subgroup.

#### **Other Discussion Points:**

- CDEC noted both GPB and NaPB are required to be used in conjunction with optimal dietary control.

- The effect of GPB on blood ammonia levels was also assessed in patients diagnosed with UCD during infancy and in those diagnosed with UCD after infancy. The results from subgroup analysis imply that adults with early onset of UCD ( $\leq 2$  years of age) responded better to GPB treatment in relation to ammonia control than adults with an onset of UCD at age 2 or older, although the number of patients in the subgroups was small and thus limited the conclusions with respect to the effect of GPB in the subpopulations.

### **Background:**

Ravicti (glycerol phenylbutyrate [GPB]) is a triglyceride containing three molecules of phenylbutyric acid (PB). Its major metabolite, phenylacetic acid, conjugates with glutamine (which contains two molecules of nitrogen) through acetylation in the liver and kidneys to form phenylacetylglutamine (PAGN). PAGN provides an alternate vehicle for waste nitrogen excretion and is excreted by the kidneys. GPB has a Health Canada–approved indication as a nitrogen-binding drug for chronic management of adult and pediatric patients  $\geq 2$  years of age with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

GPB is available as 1.1 g/mL oral liquid. It is taken orally, using nasogastric or gastrostomy tubes for patients who cannot swallow. An initial estimated GPB dose for a 24-hour period is 0.6 mL GPB per gram of dietary protein ingested per 24-hour period. The recommended total daily dose range of GPB is 4.5 mL/m<sup>2</sup>/day to 11.2 mL/m<sup>2</sup>/day (5.0 g/m<sup>2</sup>/day to 12.4 g/m<sup>2</sup>/day) with the total daily dose divided into equal amounts and given with each meal or feeding. The recommended starting doses for patients switching from NaPB to GPB and patients naive to phenylbutyrate (PB) may be different. Patients switching from NaPB to GPB should receive a GPB dose that contains the same amount of PB.

### **Summary of CDEC Considerations:**

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of GPB for the treatment of UCDs, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with UCDs.

### **Patient Input Information:**

One patient group, the Canadian Organization for Rare Disorders, responded to the CDR call for patient input. Information for the patient input submission was obtained from one-on-one interviews with patients and parents, leaders of patient advocacy groups in the US, health care professionals, surveys, websites, and emails from both Canada and the US. CDEC heard:

- Patients and caregivers reported that UCDs cause a variety of serious problems. Some of the more common symptoms are abdominal difficulties (cramps, diarrhea, vomiting, etc.) and fatigue. Patients often have developmental and cognitive problems that affect their school performance and their ability to work.
- Only a handful of patients and caregivers reported experience with NaPB (Pheburane). Some of them reported logistical problems related to its relatively short shelf life and the number of bottles needed for it when in liquid form.
- Of the survey respondents and interviewees, 87% were either currently taking GPB or had taken it in the past. The respondents reported more stable ammonia levels with GPB and no difficulties taking the drug. Most reported either no side effects or easily managed ones.

Some respondents who took GPB as part of a trial were concerned about having continued access to GPB.

### **Clinical Trials**

The CDR systematic review included one phase III, double-blind, crossover, active controlled RCT: HPN-100-006 (N = 46). The primary objective of this study was to assess the non-inferiority of GPB to NaPB by evaluating blood ammonia levels in adult patients with UCDs. In this study, eligible patients who were on stable dose of NaPB for at least one week before study entry were randomized to receive double-blind treatment of two-week NaPB followed by two-week GPB, or two-week GPB followed by two-week NaPB. For safety considerations, there were no washout periods between treatments. Additionally, evidence from three long-term, non-comparative trials (Studies HPN-100-005, HPN-100-007 and HPN-100-012) that evaluated the safety and efficacy of GPB in adult and/or pediatric patients with UCDs was reviewed.

### **Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Mortality
- Hyperammonemic crises: defined as clinical symptoms associated with ammonia levels  $\geq 100 \mu\text{mol/L}$
- Plasma ammonia levels
  - 24-hour area under the curve ( $\text{AUC}_{0-24}$ ) for blood ammonia on days 14 and 28 (the end of each treatment period) this was the primary outcome measure in Study HPN-100-006
  - maximum blood ammonia values ( $C_{\text{max}}$ ) observed on NaPB versus GPB
  - percentage of blood ammonia values above the upper limit of normal (ULN) on NaPB versus GPB.
- Safety: serious adverse events, total adverse events, and withdrawal due to adverse events.

Clinical outcomes including cognitive development, anthropometric measurements, hospitalizations, and health-related quality of life were not evaluated in the double-blind phase of Study HPN-100-006.

### **Efficacy**

- No deaths occurred during the double-blind treatment period.
- No patients had a hyperammonemic crisis during GPB treatment. One patient on NaPB treatment had a hyperammonemic crisis related to non-compliance with therapy.
- The mean  $\text{AUC}_{0-24}$  values for blood ammonia were 12% lower with GPB treatment compared with NaPB treatment ( $868.29 \pm \text{SD}668.145$  versus  $985.47 \pm \text{SD}873.578 \mu\text{mol/hour/L}$ , respectively); ratio of geometric means and 95% confidence intervals [CIs], 0.90 [-0.79 to 1.03]). GPB achieved non-inferiority to NaPB as the upper bound of the 95% CI of the ratio of the geometric means of blood ammonia  $\text{AUC}_{0-24}$  between GPB and NaPB was 1.03 (below the pre-defined non-inferiority margin of 1.25).
- 24-hour  $C_{\text{max}}$  values for blood ammonia were 14% lower with GPB treatment compared with NaPB treatment ( $60.94 \pm \text{SD}46.213$  versus  $70.83 \pm \text{SD}66.71 \mu\text{mol/L}$ , respectively). The between-group difference did not reach statistical significance; in addition, the approximately  $10 \mu\text{mol/L}$  difference in maximum blood ammonia level would not be considered a clinically meaningful change.

- The number of ammonia samples above the ULN was similar with GPB and NaPB treatments (35.6% and 36.2% of samples, respectively).
- Findings from three longer-term, open-label, non-comparative studies suggested that after one year of treatment with GPB, the effects of GPB on blood ammonia and glutamine levels appeared to be maintained in both children and adults. In addition, the number of hyperammonemic episodes per patient was reduced compared with the values 12 months before screening. Health-related quality of life, using generic quality of life assessment tools, improved in children while it appeared to decrease in adults. Neuropsychological testing results were inconsistent across trials, age groups, and assessment tools.

### **Harms (Safety and Tolerability)**

- During the four--week treatment, the proportion of patients reporting an adverse event (AE) was higher in the GPB group compared with NaPB group: 61.4% versus 51.1%, respectively. Most AEs were considered mild in intensity.
- Two patients reported treatment-emergent serious adverse events: one reported acute gastroenteritis on GPB treatment, and the other experienced a grade 3 hyperammonemia event while on NaPB treatment.
- No patients discontinued from GPB treatment; one patient discontinued from NaPB treatment because of high ammonia levels on day 1.
- In the longer-term extension studies, almost all patients experienced AEs after one year of treatment with GPB. Infections, infestations, and gastrointestinal tract disorders were the most frequently experienced AEs.

### **Cost and Cost-Effectiveness**

GPB is available as an oral liquid formulation, with total daily dosage based on body surface area and prior dosage of NaPB when patients are switching from NaPB to GPB. It is administered in equal amounts 3 to 6 times daily with food. At the manufacturer–submitted price of \$48 per mL, the monthly cost of treatment ranges from \$4,565 (young than 2 years old) to \$19,674 (18 years of age and older).

The manufacturer submitted a cost-utility analysis conducted during a patient’s lifetime (up to 100 years of age) from a Canadian public-payer perspective. The manufacturer’s base-case analyses compared GPB with either NaPB or dietary control alone. Four patient subgroups were considered:

1. Disease onset after 2 years old, and no prior treatment with NaPB or currently on treatment with NaPB. Comparator: NaPB.
2. Disease onset after 2 years old, and previously treated with NaPB but discontinued treatment due to uncontrolled ammonia level or unable to tolerate NaPB. Comparator: dietary control alone.
3. Disease onset between birth and 2 years old, and no prior treatment with NaPB or currently on treatment with NaPB. Comparator: NaPB.
4. Disease onset between birth and 2 years old, and previously treated with NaPB but discontinued treatment due to uncontrolled ammonia level or unable to tolerate NaPB. Comparator: dietary control alone.

The comparative efficacy of GPB versus NaPB was based on a pooled analysis of one double-blind crossover trial (HPN-100-006), and three open-label fixed sequence switchover trials (HPN-100-005, HPN-100-012 and UP 1204-003). Efficacy data for patients on dietary control was obtained from an observational study. The economic model considered as main health

states hyperammonemic crises, liver transplant, and death. In the base-case analyses, the manufacturer reported that the incremental cost-utility ratios (ICURs) were in excess of \$1,000,000 in three of four subgroups considered, and above \$500,000 in the remaining one (subgroup 4).

CDR identified a number of limitations with the submitted model:

- The clinical efficacy estimate used in the model for GPB, NaPB, and dietary control alone was ammonia level. Rates of hyperammonemic crises were estimated based on predicted relationships, which are highly uncertain, and were remodelled by CDR.
- The methodological quality of several model elements (such as probability of liver transplant and conduct of probabilistic analysis) was poor and contained a number of errors.
- The model is largely based on clinical opinion for which the uncertainty was not always assessed, and it is unclear to what degree this may have biased results.

Correcting the model methodological flaws and remodelling the relationship between short-term ammonia levels and hyperammonemic crises resulted in an ICUR of above \$1,000,000 per quality-adjusted life-year (QALY) for GPB versus NaPB or dietary control alone, in all subgroups considered. In order for the ICUR for GPB versus NaPB or dietary control alone to reach an ICUR of \$200,000 per QALY, the price of GPB would need to be reduced by 30% to 53% for the subgroups identified by the manufacturer. The price of GPB is 46% higher than the price of NaPB (Pheburane).

### Research Gaps:

- There is a lack of longer-term comparative efficacy and safety data available for GPB in the study population.
- There are no RCTs to compare the efficacy and safety of GPB with NaPB in pediatric patients with UCDS.

### CDEC Members:

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### February 15, 2017 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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