Common Drug Review

Pharmacoeconomic Review Report

April 2017

Drug	Glycerol phenylbutyrate (Ravicti)
Indication	Use as a nitrogen-binding agent for chronic management of adult and pediatric patients ≥2 years of age with urea cycle disorders who cannot be managed by dietary protein restriction and/or amino acid supplementation alone
Reimbursement request	As per indication
Dosage form(s)	Oral liquid, 1.1 g/mL
NOC Date	March 18, 2016
Manufacturer	Horizon Therapeutics Canada

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ABBREVIATIONS

CDR	CADTH Common Drug Review
GPB	glycerol phenylbutyrate
HAC	hyperammonemic crisis
ICUR	incremental cost-utility ratio
NaPBA	sodium phenylbutyrate
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
UCD	urea cycle disorder

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Glycerol phenylbutyrate (Ravicti)
Study Question	From the perspective of the Canadian health care system, what is the incremental cost-effectiveness of glycerol phenylbutyrate compared with standard of care in the treatment of adult and pediatric patients greater than and equal to two years of age with urea cycle disorders (UCDs) which cannot be managed by dietary protein restriction and/or amino acid supplementation alone?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Four subgroups of the indicated population were assessed: Adult and pediatric patients ≥ 2 years of age with UCDs that cannot be managed by dietary protein restriction and/or amino acid supplementation alone: • with no prior treatment with sodium phenylbutyrate or currently on treatment with sodium phenylbutyrate (Subgroup 1, disease onset after 2 years old; Subgroup 3, disease onset between birth and 2 years old) • previously treated with sodium phenylbutyrate but discontinued treatment due to uncontrolled ammonia level or inability to tolerate sodium phenylbutyrate (Subgroup 2, disease onset after 2 years old; Subgroup 4, disease onset between birth and 2 years old)
Treatment	Glycerol phenylbutyrate oral liquid 1.1 g/mL, dosage based on body surface area or prior sodium phenylbutyrate dosage
Outcome	QALYs
Comparators	• Dietary control alone (for Subgroup 2 and Subgroup 4) • Sodium phenylbutyrate (Pheburane; for Subgroup 1 and Subgroup 3)
Perspective	Canadian public payer
Time Horizon	Lifetime horizon (up to 100 years of age)
Manufacturer's Results for Base Case	Considering all subgroups assessed, results from the probabilistic analysis suggest ICURs for glycerol phenylbutyrate between around $720,000 and $6,300,000 per QALY
Key Limitations and CDR Estimate(s)	• The model's main limitations relate to the lack of natural history and treatment progression data presented on UCDs, which led to the use of very uncertain data and of assumptions that were not always appropriately justified. Additionally, the methodological quality of several model elements (such as the correlation of ammonia levels with HAS; the application of liver transplant data; the probabilistic analysis) was poor. However, correcting most of the model flaws that could be fixed does not appear to substantially affect the ICURs, except when varying the simulated relationship between short-term ammonia levels and HAC. When correcting the model methodological flaws and remodelling the relationship between short-term ammonia levels and HAC as appropriately as possible with the data available, results from the probabilistic analysis suggests ICUR for glycerol phenylbutyrate between around $1,000,000 and $2,550,000 per QALY • The manufacturer assumed that patients were treated over a lifetime and that the effect of treatment was maintained during this period. If this maintenance of effect is not accurate, this would have overestimated the ICURs in favour of glycerol phenylbutyrate. In addition, a stopping rule for treatment was not implemented. The direction of the impact of such a rule on the cost-effectiveness results is unknown.

CDR = CADTH Common Drug Review; HAS = hyperammonemic crisis; ICUR = incremental cost-utility ratios; QALY = quality-adjusted life-year; UCD = urea cycle disorder.

EXECUTIVE SUMMARY

Background

Glycerol phenylbutyrate (GPB) (Ravicti) is a sodium-free, liquid-based therapy indicated for adult and pediatric patients more than two years old with urea cycle disorders (UCDs). The total daily dosage is based on body surface area and prior dosage of sodium phenylbutyrate (NaPBA) when patients switch from NaPBA to GPB. It is administered in equal amounts three times to six times daily with food.[1] It is intended for use as an ongoing daily treatment for those with UCDs, but is not indicated or intended for use during hyperammonemic crises (HACs). The manufacturer submitted a price of $48 per mL, with estimated monthly costs of treatment ranging from $4,565 (under two years old) to $19,674 (18 years of age and older).[2]

The manufacturer is seeking reimbursement in line with the Health Canada indication.

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

- Subgroup 1: Patients with no prior treatment with NaPBA or currently on treatment with NaPBA with disease onset after two years old. This subgroup compared GPB with NaPBA (Pheburane).
- Subgroup 2: Patients previously treated with NaPBA but who discontinued treatment due to uncontrolled ammonia levels or were unable to tolerate NaPBA, with disease onset after two years old. This subgroup compared GPB with dietary control alone.
- Subgroup 3: Patients with no prior treatment with NaPBA or currently on treatment with NaPBA, with disease onset between birth and two years old. This subgroup compared GPB with NaPBA (Pheburane).
- Subgroup 4: Patients previously treated with NaPBA but who discontinued treatment due to uncontrolled ammonia levels or were unable to tolerate NaPBA, with disease onset between birth and two years old. Average starting age in the model is eight years old. This subgroup compared GPB with dietary control alone.

Evidence for the comparative efficacy of GPB versus NaPBA 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, -012, and UP 1204-003). Efficacy data for patients on dietary control were from an observational study.[3]

In the base-case analyses, the manufacturer reported that GPB is unlikely to be cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY). Incremental cost-utility ratios (ICURs) were in excess of $1,000,000 in three of four subgroups considered, and more than $500,000 in the remaining one (Subgroup 4).

Summary of Identified Key Limitations

CADTH Common Drug Review (CDR) identified a number of limitations with the submitted model:

- The estimates of effectiveness for GPB, NaPBA, and dietary control alone used in the model are based on trial results on ammonia levels, and the rate of HAC was estimated based on an existing estimate of the relationship between ammonia levels and these crises. The method used to compute this relationship is highly uncertain and was remodelled and optimized by CDR.

- The methodological quality of several model elements (such as the application of liver transplant data and the probabilistic analysis) was poor and contained a variety of errors, some of which were fixable, whereas others were not.
- 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.

Key Results and Conclusions

While the CDR analysis of the model revealed multiple flaws, most of these flaws do not appear to substantially affect the ICURs. The exception to this was modifying the simulated relationship between short-term ammonia levels and HAC.

Correcting the model's methodological flaws (such as the application of liver-transplant data and the probabilistic analysis) and remodelling the relationship between short-term ammonia levels and HAC resulted in an ICUR of more than $1,000,000 per QALY for GPB versus NaPBA or dietary control alone, in all cases considered. The subgroups for which GPB was the most cost-effective were, in order, Subgroup 2 and Subgroup 4 versus dietary control alone, onset after two years old and from birth to two years old, respectively; then Subgroup 3 and Subgroup 1 versus NaPBA (Pheburane), onset from birth to two years old and after two years old, respectively. In order for the ICUR for GPB versus NaPBA or dietary control alone to reach an ICUR of $200,000 per QALY, the price of GPB would need to be reduced by from 30% to 53% (Table 6) for the subgroups identified by the manufacturer.

The manufacturer assumed that patients were treated over a lifetime and that the effect of treatment was maintained during this period. If this maintenance of effect is not accurate, this would have overestimated the ICURs in favour of GPB. In addition, a stopping rule for treatment was not implemented. The direction of the impact of such a rule on the cost-effectiveness results is unknown.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PE SUBMISSION

The manufacturers have provided a semi-Markov model to consider the cost-effectiveness of glycerol phenylbutyrate (GPB) in four distinct subgroups:

- Subgroup 1: Patients with no prior treatment with sodium phenylbutyrate (NaPBA) or currently on treatment with sodium phenylbutyrate, with disease onset after two years old. Average starting age in the model is four years old.
- Subgroup 2: Patients previously treated with NaPBA but who discontinued treatment due to uncontrolled ammonia levels or were unable to tolerate NaPBA, with disease onset after two years old. Average starting age in the model is 20 years old.
- Subgroup 3: Patients with no prior treatment with NaPBA or currently on treatment with sodium phenylbutyrate, with disease onset between birth and two years old. All patients entered the model (as provided) at birth.
- Subgroup 4: Patients previously treated with NaPBA but who discontinued treatment due to uncontrolled ammonia levels or were unable to tolerate NaPBA, with disease onset between birth and two years old. Average starting age in the model is eight years old.

In Subgroup 1 and Subgroup 3, GPB was compared with NaPBA, while dietary control alone was used as a comparator for Subgroup 2 and Subgroup 4. The perspective of the analysis was from the Canadian health care system (payer perspective), and health benefits were reported in quality-adjusted life-years (QALYs).

The schematic for this model is provided as Figure 1 of APPENDIX 3. In the base-case, this model considered six health states, and the main event modelled was hyperammonemic crisis (HAC). As well as requiring costly treatment, these events were modelled to include a possibility of death, and those who had experienced one or more crises were modelled as separate groups from those who had never experienced a crisis.

All patients in Subgroup 2 and Subgroup 4 were assumed to have had a HAC previously and began in the "Post-HAC" health state. From this state, patients could remain in this state, transit to the "HAC" state, die (to "Other death"), or receive a transplant ("Liver transplant"). After a HAC, the patients could return to the "Post-HAC" state, die ("HAC-related death"), or receive a transplant. Both death states ("HAC-related death" and "Other death") and the "Liver transplant" state were modelled as absorbing states.

For the other subgroups, the model is broadly similar. With the exception of starting age, the only difference in modelling was that 30% of patients in Subgroup 1 and 10% of patients in Subgroup 3 did not have a HAC before they become eligible for GPB. The model for Subgroup 1 and Subgroup 3 allows this portion of patients to start in a "No previous HAC" state, with the remainder starting in the "Post-HAC" state. Once in that state, they were assumed to remain there until a first HAC (or death, or transplant) occurred.

Within the economic model, the short-term success of treatments lies in reducing the probability of HACs and, in the longer term, success was based on reduction in mortality following HACs. While the model considers the possibility of chronic conditions following HACs (as a form of disease progression), this was presented only in a sensitivity analysis.

Short-term clinical effectiveness was based on an estimation of the impact of treatments on ammonia levels from short-term trials.[2] Evidence for the comparative efficacy of GPB versus NaPBA regarding ammonia levels 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, -012, and UP 1204-003). Ammonia-level data for patients on dietary control were from an observational study.[3] In order to obtain an estimate of HAC rates, the manufacturer reanalyzed an existing estimated relationship using methods differing from the analysis that produced the estimated relationship. Raw data[4] were available to base estimates on, but were not used by the manufacturer directly.

Drug monthly costs for GPB and Buphenyl (NaPBA) were provided by Horizon Pharma, with the cost of Pheburane (NaPBA) based on Quebec list prices.[2] In the base-case analysis, only Pheburane was compared with GPB, as equivalent efficacy for Buphenyl and Pheburane was assumed, with Pheburane being cheaper. The monthly costs of treatment for GPB (based on body surface area) and Pheburane (based on weight for those < 20 kg, and surface area for those > 20 kg) increases with age.

TABLE 2: DRUG ACQUISITION COSTS BY AGE OF PATIENT WITH UREA CYCLE DISORDER

Age	GPB (Ravicti)	Pheburane
< 2 years old	$4,564.73	$2,487.72
2 to < 6 years old (20 kg cut-off)	$7,709.91	$4,893.62
6 to < 12 years old	$11,869.81	$6,925.32
12 to < 18 years old	$17,826.40	$10,400.62
≥ 18 years old	$19,674.04	$11,478.61

GPB = glycerol phenylbutyrate.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Health-state costs were based on the cost of maintenance in non-HAC states, costs of HACs, and costs of liver transplantation. A large number of assumptions were used to construct these estimates. The HAC cost was based on a microcosting of treatment (Ammonul, L-arginine) and hospital stays (general ward and intensive care units). In all cases, HACs were costly, with first HACs ranging from around $69,000 to $147,000 and subsequent HACs costing between $42,000 and $120,000 per event. Following HACs, monthly maintenance costs were assessed at $10 for adults, and around $74 to $79 for children. Liver-transplantation costs were based on a published figure from Alberta.[2]

For details on data sources and manufacturer's assumptions, refer to APPENDIX 3.

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case results (reported from the probabilistic sensitivity analysis [PSA]) are summarized in Table 3. This analysis probabilistically varied survival following HAC events, liver-transplant probabilities among patients with neonatal onset, and costs for both HAC events and urea cycle disorder (UCD) management.

TABLE 3: MANUFACTURER'S RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,577,069	9.75			
GPB	$3,890,748	9.96	$1,313,678	0.21	$6,284,086
SUBGROUP 2					
DC	$2,242,602	7.63			
GPB	$4,442,373	9.57	$2,199,771	1.94	$1,132,758
SUBGROUP 3					
NaPBA	$1,823,945	9.41			
GPB	$2,695,769	9.58	$871,824	0.16	$5,294,691
SUBGROUP 4					
DC	$2,222,341	7.82			
GPB	$3,542,844	9.66	$1,320,503	1.84	$718,620

DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

In all four of the subgroups, GPB is suggested to become the most cost-effective option only at values far above an indicative cost per QALY threshold of $50,000. In three of the four subgroups, this figure exceeds $1 million per QALY, with the two subgroups comparing GPB with NaPBA having incremental cost-utility ratios (ICURs) exceeding $5 million per QALY.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Alongside the PSA, the manufacturer provided tornado diagrams displaying one-way sensitivity analyses for those variables that were varied in the probabilistic analyses. Within the 88 scenario analyses considered, there were only three scenarios in which GPB would be considered cost-effective at a threshold of $500,000 per QALY (i.e., at 10 times an indicative threshold of $50,000 per QALY). In two of these cases, Buphenyl (rather than Phenurate) was used as the NaPBA alternative and, in these cases, GPB dominated. In the remaining case, among patients with late-onset UCD who could not receive NaPBA, the relative risk of HACs was assumed to be 10.5 times the rate for those receiving dietary control (up from 8.42), and, in this case, GPB produced QALYs at a cost of $480,733 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

The main limitation of the manufacturer's submission relates to the lack of data presented on UCDs. This has led the manufacturer to use a reasonably simple model structure and to populate this structure with extrapolated relationships between outcomes and clinical opinions. In some cases, this appears to be due to the rare nature of UCDs, but at several points assumptions do not appear to be justified.

The manufacturer's model contains multiple flaws:

- The primary outcomes reported from the clinical trials of GPB and NaPBA were ammonia levels. The manufacturer cites an estimated relationship found between ammonia levels and HACs, and uses linear interpolation between these two estimated points to further estimate HAC risks for dietary control. The points that the manufacturer uses to estimate a linear relationship (at differences of 10 µmol/L and 25 µmol/L versus GPB) are small compared with the difference (91.7 µmol/L versus GPB) then used to estimate a relative risk for dietary control versus GPB. As an approach, this is flawed, and the manufacturer's submission on this point is discussed in more detail in Appendix IV.
- The probability of liver transplantation is estimated based on the reanalysis of a single paper reporting the ages at which liver transplantation occurs. The probabilities used appear to be based on a flawed interpretation of the data provided and underestimate the true probabilities, especially among older patients, as a result of both mortality and censoring.
- The parameters drawn within the manufacturer's PSA are flawed. The model inappropriately uses normal distributions to draw cost parameters, where gamma or lognormal distributions should be used instead, as the distributions should be skewed. When estimating the relative risks of HACs, the model uses lognormal distributions but incorrectly identifies these distributions by setting the mean of the lognormal distribution to the logarithm of the mean costs.
- The PSA does not include all items that might be allowed to vary, given the available data. Where these are allowed to vary, only 1,000 model runs were considered. Given the large amount of uncertainty about key outcomes (such as the relative risk of HACs), a higher number of model runs is likely to be necessary to provide clear results.
- In Subgroup 3, the estimated starting age for treatment is at birth, while the indication is for patients aged two and older. The subgroup age should be at least two years of age.

The manufacturer identifies that adherence to NaPBA is difficult for many patients. However, adherence was not considered an issue within the model. Normally, this would appear to be a conservative assumption favouring alternative treatments and disadvantaging GPB. However, in this case, the impact of this is likely to be increased cost-effectiveness of GPB versus NaPBA, since (1) this does not consider the possibility that GPB will not be tolerated and (2) the alternative treatment (dietary control) appears to be more cost-effective generally than either GPB or NaPBA.

There were some comments from the clinical expert consulted by CADTH Common Drug Review (CDR) that the main clinical study for GPB (versus NaPBA) may have recruited patients who have somewhat less severe UCD than the general patient population. This may have the effect that the benefits of GPB versus NaPBA may be accurate within the group considered but underestimated overall, since there may be greater benefits in more severe phenotypes (or mix of phenotypes). This cannot be fully assessed with the data provided, since this reflects the trials submitted. It is worth noting, however, that the subgroup used in the economic analysis to represent dietary control represent a group of patients with higher ammonia levels who may have a more severe mix of phenotypes than those recruited in the GPB trials. If this is the case, there is a danger that naive indirect treatment comparisons of the type necessary (given the lack of head-to-head data or analysis of patient-level data) may over-estimate the cost-effectiveness of GPB versus dietary control.

5. CADTH COMMON DRUG REVIEW REANALYSES

The manufacturer's submission was modified in the following ways:

- The probability of liver transplantation in patients with early-onset UCD (Subgroup 3 and Subgroup 4) was changed, first, by correcting the calculation of monthly probabilities from underlying rates. It is not possible to correct for issues around mortality and censoring in full; but it is likely that these issues are greater in the probabilities the manufacturer uses for those aged 24 and older versus for those aged 12 years to 24 years. Hence, the probability of transplantation for those aged 24 and older was set to the same probability as used for those aged 12 years to 24 years.
- The probabilities of liver transplantation for patients with late-onset UCD (Subgroup 1 and Subgroup 2) use the manufacturer's assumption of a relative risk of 0.2 versus those with early-onset UCD. The manufacturer did not probabilistically vary this estimate, but CDR did so on the basis of the uncertainty of the estimate.
- The cost parameters that were assessed as normally distributed are now more appropriately drawn from lognormal distributions.
- The errors in the drawing of lognormal distributions for relative risks of HACs were modified so that the intended distribution is drawn.
- In Subgroup 3, the starting age of the cohort was modified to be two years of age.
- The model was modified to allow the PSA to include 10,000 model runs.

The results of this first reanalysis are provided in Table 4. These results are broadly similar to those provided by the manufacturer. Again, ICURs for GPB versus NaPBA exceeded $5 million, while those for GPB versus dietary control exceeded $1 million per QALY in patients with late-onset UCD, and are between $700,000 and $800,000 per QALY in those with early-onset UCD.

TABLE 4: CDR FIRST REANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,580,167	9.81			
GPB	$3,893,845	10.02	$1,313,678	0.21	$6,214,030
SUBGROUP 2					
DC	$2,180,226	7.79			
GPB	$4,441,678	9.59	$2,261,453	1.80	$1,257,935
SUBGROUP 3					
NaPBA	$1,910,683	9.50			
GPB	$2,811,783	9.65	$901,101	0.15	$5,841,454
SUBGROUP 4					
DC	$2,063,474	7.98			
GPB	$3,333,151	9.60	$1,269,677	1.63	$780,570

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

In addition to the preceding varied for the first reanalysis, the full CDR revision of the manufacturer's model modifies the probabilities of HAC. Following the approach outlined in Appendix IV, the probabilities of HACs were re-estimated using the same data as the manufacturer provided, but using the raw data. The expected HAC rates correspond to 0.27 HAC per year on GPB (versus 0.27 in the

manufacturer's submission), 0.54 HAC per year on NaPBA (versus 0.39), and 1.76 HACs per year on dietary control (versus 2.27). This change is expected to improve the cost-effectiveness of GPB relative to NaPBA but decrease the cost-effectiveness of GPB versus dietary control.

Table 5 provides the revised analysis results. As expected, the incremental cost-effectiveness ratios for GPB are reduced in cases when patients receive NaPBA but increased when the comparison is with dietary control. The ICURs for NaPBA exceed $2 million per QALY, which is 40 times an indicative threshold of $50,000 per QALY.

TABLE 5: CDR REVISED ANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER (0% PRICE DISCOUNT)

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,719,926	9.56			
GPB	$3,895,776	10.02	$1,175,850	0.46	$2,559,450
SUBGROUP 2					
DC	$1,991,358	7.98			
GPB	$4,443,465	9.58	$2,452,107	1.60	$1,532,491
SUBGROUP 3					
NaPBA	$2,031,362	9.30			
GPB	$2,812,972	9.65	$781,610	0.34	$2,288,790
SUBGROUP 4					
DC	$1,874,190	8.16			
GPB	$3,333,535	9.60	$1,459,345	1.44	$1,012,665

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

In all cases, it is clear that GPB is not cost-effective at an indicative threshold of $50,000 per QALY. Across the 10,000 model runs underlying the PSA, none of these suggest that GPB is cost-effective (at a willingness-to-pay threshold of $50,000 per QALY) for patients receiving dietary control (i.e., Subgroup 1 and Subgroup 3). For the two subgroups in which patients received NaPBA, the likelihood that GPB is cost-effective (at a willingness-to-pay threshold of $50,000 per QALY) appears to be only 0.02% in patients with late-onset UCD (Subgroup 2) and 0.04% in those with early-onset UCD (Subgroup 4). Based on efficiency grounds, GPB would not be selected in any of the four subgroup analyses presented.

Threshold analyses are provided to identify price discounts at which GPB is likely to become cost-effective at $50,000 and $200,000 per QALY, with a summary of the ICURs produced appearing in Table 6. For the subgroups for which NaPBA is the comparator, a price reduction of around 32% (in late-onset UCD) and 30% (in early-onset UCD) for GPB would be needed for the ICUR to fall to $200,000 per QALY. To obtain an ICUR of $50,000 per QALY, a price reduction of 34% and 32%, respectively, would be required.

Higher discounts are required to attain cost-effectiveness in the subgroups for which dietary control alone is the comparator. This is because the cost of the alternative treatment (dietary control) is lower, and because dietary control represents a more cost-effective use of resources than NaPBA. In the case of those on dietary control, a discount of around 59% is necessary to obtain an ICUR of below $50,000

per QALY in patients with late-onset UCD, and 47% in patients with early-onsetUCD. Even at a higher $200,000 per QALY, the discounts necessary are still 53% and 40%, respectively.

TABLE 6: CDR REVISED ANALYSIS – THRESHOLD ANALYSIS FOR PRICE REDUCTIONS SCENARIOS

	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
	GPB vs. NaPBA ICUR ($/QALY)	**GPB vs. DC ICUR ($/QALY)**	**GPB vs. NaPBA ICUR ($/QALY)**	**GPB vs. DC ICUR ($/QALY)**
No discount	$2,559,450	$1,532,491	$2,288,790	$1,012,665
30% discount	$324,737	$779,241	$157,546	$405,100
32% discount	$173,471	$722,734	$13,665	$358,819
34% discount	$24,578	$682,118	DOMINATES	$325,418
40% discount	DOMINATES	$524,197	DOMINATES	$198,052
47% discount	DOMINATES	$347,151	DOMINATES	$53,470
50% discount	DOMINATES	$274,142	DOMINATES	DOMINATES
53% discount	DOMINATES	$196,783	DOMINATES	DOMINATES
59% discount	DOMINATES	$43,860	DOMINATES	DOMINATES

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year; vs. = versus.

6. ISSUES FOR CONSIDERATION

The manufacturer has presented a relatively simple economic model to accompany its submission. In part, this reflects the relatively rare nature of the disease. Within the disease, however, there are a large number of different subtypes, and these have not been modelled separately within the model provided. It is likely that the mix of these subtypes will differ across the four subgroups, and each subgroup presented will contain a number of different subtypes. It is unclear how the cost-effectiveness of dietary control, NaPBA, and GPB will differ *within* each subgroup, and, in the absence of information, no conclusions can be made.

It is clear, however, that the clinical evidence upon which efficacy assumptions are made did include a variety of different subtypes but possibly a different mix than that expected in clinical practice. To whatever degree this is the case, it seems unlikely to change the overall results as to the cost-effectiveness of GPB. The cost driver of the analysis is the drug acquisition costs.

When the alternative to GPB is Pheburane (per the manufacturer's submission), the incremental drug cost of GPB ranges from around $25,000 (for those aged under two) to nearly $100,000 per patient annually. As the quality of life (QoL) for patients with UCDs is estimated to be 0.55, there is no way that more than 0.55 QALYs could be produced per year, even when GPB guaranteed survival with no HACs and the alternative treatment resulted in immediate death. Here, the best possible ICURs in a calendar year under such unrealistic conditions would be around $45,500 per QALY in those aged under two years of age, increasing to $181,000 per QALY in those aged 18 and over.

This issue is even more pronounced once dietary control is considered as an alternative, as the extra cost per year of GPB is at least $55,000 in those aged under two years of age, increasing to $236,000 for those aged over 18 years of age. In this circumstance, the best possible ICURs (under the unrealistic conditions previously described) would range from $100,000 per QALY to $430,000 per QALY.
As the QoL with a successfully treated UCD cannot be changed, and these broad calculations assume an

unrealistically large clinical benefit for GPB, the only way GPB could appear even remotely cost-effective among any subgroup is through significant price reductions.

7. PATIENT INPUT

One patient group, the Canadian Organization for Rare Disorders, provided input for this submission. It was noted that UCD is a genetic condition that can manifest with variable severity and characteristics. The impact of the condition can depend on the specific genetic mutation as well as other factors (the economic analysis presented by the manufacturer did not assess subgroups based on this). Symptoms typically vary from birth to adulthood and have an important impact on patients' lives. Patients with a UCD report fatigue, lethargy, weakness, abdominal symptoms, eating disorders, serious behavioural problems, and learning or cognitive disorders. The condition has a serious impact on home and/or social life and can be associated with frequent hospitalizations. Caregivers expressed that they experienced a tremendous impact on their lives when caring for someone with a UCD.

The submitted cost-effectiveness analysis considered ammonia levels as the efficacy outcome with which QoL data (utility scores) were combined. Information on the outcomes of interest to patients were in some cases not captured in the clinical trials and not considered explicitly in the model. The manufacturer did not include the impact on caregivers in its model.

8. CONCLUSIONS

The manufacturer's submission provided an economic model in which GPB does not appear, at a willingness-to-pay threshold of $50,000 per QALY, to be cost-effective when compared with either the existing pharmaceutical option (NaPBA; Pheburane) or dietary control. The CDR analysis of this model identified many flaws, although most of the fixable flaws do not appear to substantially affect the incremental cost-effectiveness ratios, when accounted for. The exception to this was modifying the simulated relationship between short-term ammonia levels and HACs.

While the changes to the model affect estimates of cost-effectiveness, GPB does not appear to be cost-effective at a willingness-to-pay cost-effectiveness threshold of $50,000 per QALY, or at four times this figure ($200,000 per QALY). Overall, the ICURs produced in the four subgroups of interest range from $1 million per QALY to $2.55 million per QALY.

In order for the incremental cost-effectiveness of GPB to even approach small multiples of $50,000 per QALY, it appears that significant price reductions would be necessary. For the analyses comparing GPB with NaPBA, price reductions of more than 30% would be required for GPB to reach an ICUR of $200,000 per QALY. For the analyses comparing GPB with dietary control, higher price reductions of more than 50% would be required.

The manufacturer assumed that patients were treated over a lifetime and that the effect of treatment was maintained during this period. If this maintenance of effect is not accurate, this would have overestimated the ICURs in favour of GPB. In addition, a stopping rule for treatment was not implemented. The direction of the impact of such a rule on the cost-effectiveness results is unknown.

The price of GPB is 46% higher than the price of NaPBA (Pheburane).

APPENDIX 1: COST COMPARISON

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Existing product reimbursement agreements are not reflected in the table; therefore, the costs may not represent the actual costs to public drug plans.

TABLE 7: CDR COST-COMPARISON TABLE

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Glycerol phenylbutyrate (Ravicti)	**1.1 g/mL**	**oral liquid**	**48.000[a] /mL (43.6364[a]/g)**	**4.5 to 11.2 mL:/m^2/day (5 to 12.4 g/m^2/day) in 3 to 6 equally divided doses, rounded up to the nearest 0.5 mL**	**$152.16 to $655.80[b]**	**$55,012 to $239,367**
Sodium phenylbutyrate (Pheburane)	483 mg per gram of granules	granule	19.2000[c]/g	Patient weight < 20 kg: 450 mg/kg/day to 600 mg/kg/day Patient weight ≥ 20 kg: 9.9 g/m^2/day to 13.0 g/m^2/day	$82.92 to $382.62[d]	$29,853 to $137,743
Sodium phenylbutyrate (Buphenyl)	500 mg	tab powder	48.7500[e]/g	Patients weight < 20 kg: 450 mg/kg/day to 600 mg/kg/day Patient weight ≥ 20 kg: 9.9 g/m^2/day to 13.0 g/m^2/day	$210.55 to $971.50[d]	$75,798 to $349,739

CDR = CADTH Common Drug Review.
[a] Manufacturer's submission.[2]
[b] Based on average daily dose of 7.85 mL/m^2 per day and body surface areas of 0.4 m^2 (< 2 years old) and 1.72 m^2 (≥ 18 years old).[2]
[c] Association Québécoise des Pharmaciens Propriétaires (AQPP) Price List, based on manufacturer's submission.[2]
[d] Based on average daily dose of 530 mg/kg/day (patients weighing < 20kg) and 11.45g/m^2/day (≥ 20 kg). Upper and lower bounds are based on the body surface area of the youngest patients (< 2 years old, 0.4m^2) and the weight of the oldest patients (≥ 18 years old, 62.50 kg).[2]
[e] Hyperion Therapeutics Inc. US WAC price, converted to Canadian dollars, from the manufacturer's submission.[2]

APPENDIX 2: ADDITIONAL INFORMATION

TABLE 8: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 9: AUTHORS' INFORMATION

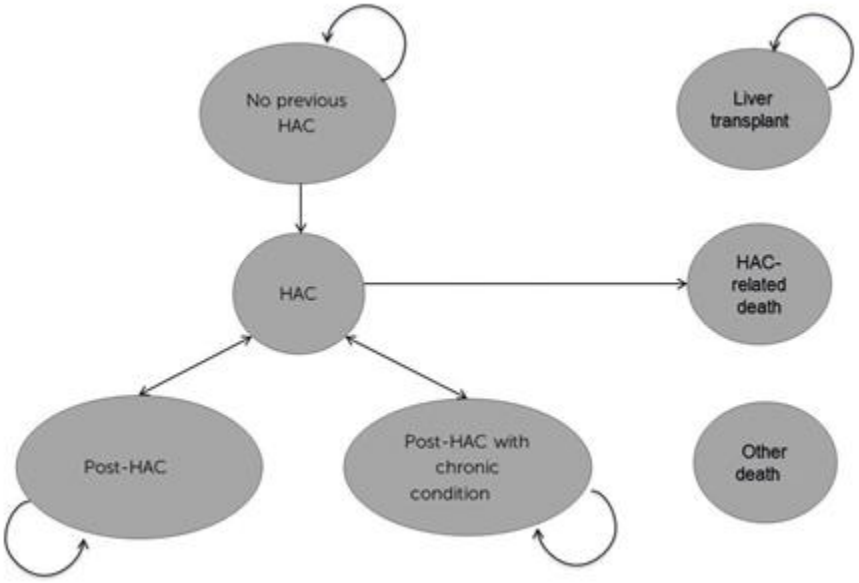
Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review			
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis		X	

APPENDIX 3: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The natural history for urea cycle disorders (UCDs) was modelled by the manufacturer using the structure in the subsequent figure.

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



HAC = hyperammonemic crisis.
Source: Manufacturer's pharmacoeconomic submission.[2]

A discussion of the model structure is provided in the main body of the CADTH Common Drug Review (CDR) pharmacoeconomic report. Treatment was incorporated into this natural history by modifying the costs of the "No previous HAC" (hyperammonemic crisis) and "HAC" states, and by modifying the probability of HAC. In this way, the changes to the model induced by treatment seek to account for how treatment modifies the natural history of the disease.

TABLE 10: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Evidence was claimed based on analysis of one week's and two weeks' trial data on short-term ammonia control, within the common technical document provided.[2] These trials include one double-blind crossover trial (HPN-100-006), and three open-label fixed-sequence switchover trials (HPN-100-005, -012, and UP 1204-003). Evidence is presented relating blood ammonia levels to risk of HAC.[4]	See note.
Natural history	Liver-transplantation probabilities based on reanalysis of a table within a single paper. One scenario analysis does consider the possibility of chronic conditions as a result of HAC, although no data were provided.	There is limited natural history in the model, although the model does include liver transplantation and HACs. There are issues with the way that these states are incorporated, as detailed subsequently.
Utilities	Clinical opinion was provided to obtain utility inputs for UCD patients (0.55), plus decrements for HAC (0.50).	All utilities were based upon clinical opinion.
Resource use	See "costs;" these were based on assumptions.	
AEs	Not considered in the model, and stated to be with the support of Canadian clinical experts[5]	
Costs		
Drug	GPB based on manufacturer's price, Pheburane on Quebec list prices	
AEs	Not considered in the model, and stated to be with the support of Canadian clinical experts[5]	Assumed to be comparable and minor
Health state	Costs for HAC states were estimated using detailed assumptions, and considered both drug treatment and hospital stays. Costs of follow-up treatments following HACs were again based on detailed assumptions, considering specialists, MRIs, dietitians, and nurse practitioners. A one-off liver-transplant cost was set at $127,700 based on data from Alberta.[2]	Given that the disease is rare, some degree of assumption is expected. However, there is no broad comparison against other international figures to give context.
End of life	End-of-life costs were assumed from a Canadian source at around $68,000 per death.[6]	The use of this cost may be controversial.

AE = adverse events; GPB = glycerol phenylbutyrate; HAC = hyperammonemic crisis; MRI = magnetic resonance imaging; UCD = urea cycle disorder.

Note: (1) The primary outcomes reported from the clinical trials of GPB and sodium phenylbutyrate were ammonia levels. The manufacturer cites an estimated relationship between ammonia levels and HACs and uses linear interpolation between these two estimated points to further estimate HAC risks for dietary control well beyond the range defined by these points (a difference of 91.7 µmol/L, versus points at 10 µmol/L and 25 µmol/L). The estimated relative risk of 8.42 for dietary control is discussed further in Appendix IV.

TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Mortality post–liver transplant based on three-year survival figures (93% survival) or background population mortality, whichever is larger	Mortality following a liver transplant is not necessarily constant over time. However, the impact is expected to be minor.
No uncertainty in liver transplant probability in patients with late-onset UCD	This appears inappropriate, as uncertainty was assumed for patients with early-onset UCD, as well as a relationship between the relative risks of both groups.
No separate state for initial and subsequent years following a liver transplant	The model applies the cost of liver transplantation only to new transplants but does not appear to apply an ongoing cost following transplantation, or to apply a different utility to the year of transplant than to following years.
Probabilistic sensitivity analysis run on 1,000 model runs.	This may be insufficient when parameters such as relative risks are modelled using lognormal distributions, as significant uncertainty exists.
Linear interpolation used to estimate HAC rates for Pheburane.	See Appendix 4
All patients receiving sodium phenylbutyrate use Pheburane.	This is not necessarily accurate but is a conservative assumption and, given the information provided (higher patient acceptability, cheaper price), seems reasonable.
No increase in utility following liver transplant	This was considered beyond the scope of the analysis by the manufacturers.
Probabilistic sensitivity analyses use normal distribution to model uncertainty in cost parameters.	This is not good practice, since cost parameters are expected to be skewed. A lognormal or gamma distribution is more appropriate.
Probabilistic sensitivity analyses assume that standard errors are 20% of mean values when data are not available.	This is relevant for liver-transplantation probabilities. It is unclear how much of an impact this has, and for some parameters this would be a very small uncertainty to assume. In probabilities, this may not be as problematic.
Liver transplantation in neonatal patients based on a simulated cohort	A single paper was used[4] to identify age of liver transplantation in a cohort diagnosed as neonates. However, most of these patients are living, and so the manufacturer's analysis that assumes that all patients survive to 100 years of age, is inappropriate. See note (1).

Assumption	Comment
Adherence is not considered in the model.	The manufacturer identifies that adherence with sodium phenylbutyrate is difficult for many patients, but the model does not fully reflect this alternative. See note (2).

HAC = hyperammonemic crisis; UCD = urea cycle disorders.
Note: (1) In order to estimate the probability of receiving a transplant among patients with early onset UCD, the manufacturer uses a paper reporting on a birth cohort of patients with a UCD. This paper reports when patients received transplants across five age bands (to 6 years, from 6 years to 12 years, from 12 years to 24 years, from 24 years to 48 years, and 48 years and over) but does not report the current age of patients. In order to obtain probabilities, the manufacturer assumes that patients survive within each of the five age bands provided, i.e., that all patients in that birth cohort have either survived to 100 years of age, or have received a liver transplant at an earlier point in time. For example, when computing a probability of liver transplantation for patients between 12 and 24 years of age, the manufacturer assumes that all patients who do not receive a liver transplant have been observed through 24 years of age. A probability of not receiving a transplant is computed by dividing the numbers of patients who have not received transplants by the age 24 by the number who had not received transplants at age 12, and further dividing this figure by 12 years to obtain a "rate" (which is itself inappropriate). As we do not know that all patients survive, and as many patients will be within that range at the time of observation, this approach is likely to underestimate the true probability of liver transplantation. The same issues are likely to be the case for all of the probabilities for liver transplantation, and especially for those aged 48 years or older; the manufacturer assumes that all of these patients somehow survived until 100 years of age, despite the higher mortality rates assumed owing to urea cycle disorder. The manufacturer assumes that the relative risk of transplantation in patients with late-onset UCD versus those with early-onset UCD is 0.2, based on clinical opinion.
(2) The impact of this is likely to unrealistically increase the cost-effectiveness of GPB versus sodium phenylbutyrate, since (1) this does not consider the possibility that GPB is not tolerated and (2) the alternative treatment (dietary control) appears to be more cost-effective generally than either GPB or sodium phenylbutyrate.

Manufacturer's Results

Table 3 provides the manufacturer's results for the probabilistic sensitivity analysis (PSA) for glycerol phenylbutyrate (GPB) in the four subgroups considered. In each of the subgroups, GPB becomes cost-effective only at incremental cost-utility ratios (ICURs) well above an indicative cost per quality-adjusted life-year (QALY) threshold of $50,000. In three of four subgroups, this figure exceeds $1 million per QALY, with the two subgroups comparing GPB with sodium phenylbutyrate (NaPBA) having ICURs exceeding $5 million per QALY.

These probabilistic results used selected parameters and produced results very similar to the deterministic analysis. This PSA was formed using 1,000 model runs, with the manufacturer's model (as provided) able to accept up to 10,000 model runs. Parameters included in the PSA are summarized in Table 12.

TABLE 12: PARAMETERS INCLUDED/NOT INCLUDED IN PSA

Type of Parameters	Included in PSA?
Starting age for patient group	No
Proportion of patients in starting health states	No
Survival following HAC	Yes
Relative risk of death (vs. general population) for UCD patients	No
Number of HACs per year, GPB	**No**
Relative risk of HACs for NaPBA vs. GPB, DC	**No**
Liver-transplant probabilities: neonatal onset	Yes
Liver-transplant probabilities: late onset	No
Utility data	**No**
Unit costs for drug costs	No
Total cost of initial or subsequent HAC	Yes
Weekly costs of management in HAC/no-HAC groups	Yes

DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; HAC = hyperammonemic crisis; NaPBA = sodium phenylbutyrate; PSA = probabilistic sensitivity analysis; UCD = urea cycle disorder; vs. = versus.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

Alongside the PSA, the manufacturer provided tornado diagrams displaying one-way sensitivity analyses for those variables that were varied in the PSA.

An additional set of scenario analyses was also conducted to assess other assumptions in the model.

TABLE 13: PARAMETERS MODIFIED IN SENSITIVITY ANALYSIS

Parameter modified	Original value	Revised value(s)
Cost of alternative treatment, using Buphenyl as a sodium phenylbutyrate treatment, as opposed to Pheburane	$48.75/g	$19.20/g
Mortality rate from liver transplantation	0.2%	0%
Relative risk of UCD patients vs. general population	3	2, 4
Relative risk of HAC for DC patients	8.42	6.5, 10.5
Utility decrement associated with HAC	0.5	0.3, 0.4
Utility associated with UCD patients	0.55	0.45, 0.65, 0.75
Relative risk of liver transplant for patients with late onset compared with neonatal onset UCD	0.02	0, 0.05, 1
Length of HAC	7	3.5, 10.5
Time horizon	To 100	1, 5, 10 years
Discounting	5%	0%, 3%

DC = dietary control plus supplementation only; HAC = hyperammonemic crisis; UCD = urea cycle disorder.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

One-way sensitivity analyses:
While the manufacturer's tornado diagrams state that they display "net benefits," it does not appear that this is the case, and instead ICURs are displayed. Overall, the changes considered in the one-way sensitivity analysis do not make the ICUR for GPB approach the indicative cost-effectiveness threshold values. For Subgroup 1 and Subgroup 3, the ICUR does not fall below $2,500,000 per QALY, whereas, for

Subgroup 2 and Subgroup 4, the ICURs remain more than $700,000 and $500,000 per QALY, respectively.

Scenario analyses:
Within the 88 different scenario analyses provided by the manufacturer, there are only three scenarios in which GPB would be considered cost-effective at a threshold of $500,000 per QALY (i.e., at 10 times an indicative $50,000 per QALY).

Table 14 displays the two scenarios in which GPB dominates alternative treatments, when NaPBA is provided using the more expensive Buphenyl option. In the base-case analysis, it is assumed that only Pheburane is used; if this is not the case, then this scenario suggests that there may be an impact on estimates of cost-effectiveness. (Note that the manufacturer submission's Table 28, which suggests that GPB is dominated, is incorrect.)

The third scenario deals with Subgroup 4. The relative risk of HAC is assumed to be 10.5 times for those receiving dietary control versus GPB. In this case, the ICUR is $480,733, with details in Table 14.

TABLE 14: SELECTED SCENARIO ANALYSES

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1: Comparison using Buphenyl as NaPBA treatment					
GPB	$3,889,822	9.95			DOMINANT
NaBPA	$5,569,020	9.74	$1,679,198	-0.21	
SUBGROUP 3: Comparison using Buphenyl as NaPBA treatment					
GPB	$2,691,796	9.55			DOMINANT
NaBPA	$3,870,328	9.38	$1,178,532	-0.16	
SUBGROUP 4: Relative risk of HAC for DC vs. GPB of 10.5 (vs. 8.42)					
DC	$2,484,085	7.44			
GPB	$3,537,080	9.63	$1,052,995	2.19	$480,733

DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; HAC = hyperammonemic crisis; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year; vs. = versus.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[2]

In a sensitivity analysis, a separate "Post-HAC with chronic condition" state was added to the model, assuming that 50% of those who enter the model would have previously experienced a HAC and would begin in this state. In the model, an individual beginning a period in a post-HAC no chronic condition could transit to HAC, and then have a 50% chance (if surviving and not receiving a transplant) of being in either post-HAC (no chronic condition) or "Post-HAC with chronic condition." However, the way this is coded also means that same individual could, after having a HAC, have a 50% chance (if surviving and not receiving a transplant) of returning to "Post-HAC no chronic condition." This appears inappropriate, as a HAC may cure a chronic condition. While this is a potentially important issue in terms of the disease progression, the manufacturer's model cannot address this without more data and substantial changes to the submitted model.

CADTH Common Drug Review Reanalyses

Several concerns were raised surrounding the manufacturer's submission. These were modified in the ways identified within the main body of this report. In order to implement the threshold analysis, the final model was run with a 0%, 30%, 40%, and 50% price discount for GPB. Based on these results, the ICUR values were interpolated to identify likely price discounts at which each subgroup would likely "reach" a cost per QALY of $200,000 per QALY.

The CDR intermediate reanalysis provides findings relatively similar to the original manufacturer's analysis, although the ICURs for GPB are generally slightly higher than those reported by the manufacturer.

TABLE 15: CDR INTERMEDIATE REANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,580,167	9.81			
GPB	$3,893,845	10.02	$1,313,678	0.21	$6,214,030
SUBGROUP 2					
DC	$2,180,226	7.79			
GPB	$4,441,678	9.59	$2,261,453	1.80	$1,257,935
SUBGROUP 3					
NaPBA	$1,910,683	9.50			
GPB	$2,811,783	9.65	$901,101	0.15	$5,841,454
SUBGROUP 4					
DC	$2,063,474	7.98			
GPB	$3,333,151	9.60	$1,269,677	1.63	$780,570

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

It is noticeable, however, that the revised analysis differs from the "intermediate" one. As predicted, the cost-effectiveness of GPB relative to NaPBA has increased (although it does not fall below $2,000,000 per QALY), but the cost-effectiveness of GPB relative to dietary control has decreased.

TABLE 16: CDR REVISED ANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER (0% PRICE DISCOUNT)

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,719,926	9.56			
GPB	$3,895,776	10.02	$1,175,850	0.46	$2,559,450
SUBGROUP 2					
DC	$1,991,358	7.98			
GPB	$4,443,465	9.58	$2,452,107	1.60	$1,532,491
SUBGROUP 3					
NaPBA	$2,031,362	9.30			
GPB	$2,812,972	9.65	$781,610	0.34	$2,288,790
SUBGROUP 4					
DC	$1,874,190	8.16			
GPB	$3,333,535	9.60	$1,459,345	1.44	$1,012,665

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

TABLE 17: CDR REVISED ANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER (30% PRICE DISCOUNT)

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,720,038	9.56			
GPB	$2,867,735	10.02	$147,697	0.45	$324,737
SUBGROUP 2					
DC	$1,999,730	7.99			
GPB	$3,239,014	9.58	$1,239,283	1.59	$779,241
SUBGROUP 3					
NaPBA	$2,030,343	9.31			
GPB	$2,083,521	9.65	$53,177	0.34	$157,546
SUBGROUP 4					
DC	$1,876,453	8.17			
GPB	$2,456,356	9.60	$579,903	1.43	$405,100

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

TABLE 18: CDR REVISED ANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER (40% PRICE DISCOUNT)

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,716,249	9.56			
GPB	$2,523,318	10.02	–$192,931	0.46	DOMINATES
SUBGROUP 2					
DC	$1,992,783	7.98			
GPB	$2,833,968	9.58	$841,185	1.60	$524,197
SUBGROUP 3					
NaPBA	$2,028,919	9.31			
GPB	$1,840,787	9.65	–$188,132	0.34	DOMINATES
SUBGROUP 4					
DC	$1,877,778	8.15			
GPB	$2,164,177	9.60	$286,399	1.45	$198,052

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

TABLE 19: CDR REVISED ANALYSIS – RESULTS FOR PATIENTS WITH UREA CYCLE DISORDER (50% PRICE DISCOUNT)

	Costs	QALYs	Incremental Costs	Incremental QALYs	ICUR ($/QALYs)
SUBGROUP 1					
NaPBA	$2,718,236	9.57			
GPB	$2,179,612	10.02	–$538,625	0.46	DOMINATES
SUBGROUP 2					
DC	$1,993,102	7.99			
GPB	$2,431,138	9.59	$438,036	1.60	$274,142
SUBGROUP 3					
NaPBA	$2,029,828	9.31			
GPB	$1,596,349	9.65	–$433,478	0.34	DOMINATES
SUBGROUP 4					
DC	$1,876,895	8.16			
GPB	$1,869,395	9.60	–$7,500	1.44	DOMINATES

CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year.

In the base-case analysis, the ICURs for NaPBA exceed $2 million per QALY, which is 40 times an indicative threshold of $50,000 per QALY. For those currently prescribed NaPBA, the price of GPB would need to be discounted by around 32% (late onset) and 30% (early onset) to obtain even an ICUR of $200,000 per QALY. To obtain an ICUR at an indicative threshold of $50,000 per QALY, these discounts would need to increase to 34% and 32%, respectively.

Higher discounts are required to obtain cost-effectiveness for those who do not tolerate NaPBA. This is because the cost of the alternative treatment (dietary control) is lower, and because dietary control represents a more cost-effective use of resources than NaPBA. In the case of those on dietary control, a discount of around 59% is necessary to obtain an ICUR below $50,000 per QALY in patients with late-

onset UCD, and 47% in those with early-onset UCD. Even at a higher $200,000 per QALY figure, the discounts necessary are still 53% and 40%, respectively.

TABLE 20: CDR REVISED ANALYSIS – THRESHOLD ANALYSIS FOR DISCOUNTS

	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
	GPB vs. NaPBA ICUR ($/QALY)	**GPB vs. DC ICUR ($/QALY)**	**GPB vs. NaPBA ICUR ($/QALY)**	**GPB vs. DC ICUR ($/QALY)**
No discount	$2,559,450	$1,532,491	$2,288,790	$1,012,665
30% discount	$324,737	$779,241	$157,546	$405,100
32% discount	$173,471	$722,734	$13,665	$358,819
34% discount	$24,578	$682,118	DOMINATES	$325,418
40% discount	DOMINATES	$524,197	DOMINATES	$198,052
47% discount	DOMINATES	$347,151	DOMINATES	$53,470
50% discount	DOMINATES	$274,142	DOMINATES	DOMINATES
53% discount	DOMINATES	$196,783	DOMINATES	DOMINATES
59% discount	DOMINATES	$43,860	DOMINATES	DOMINATES

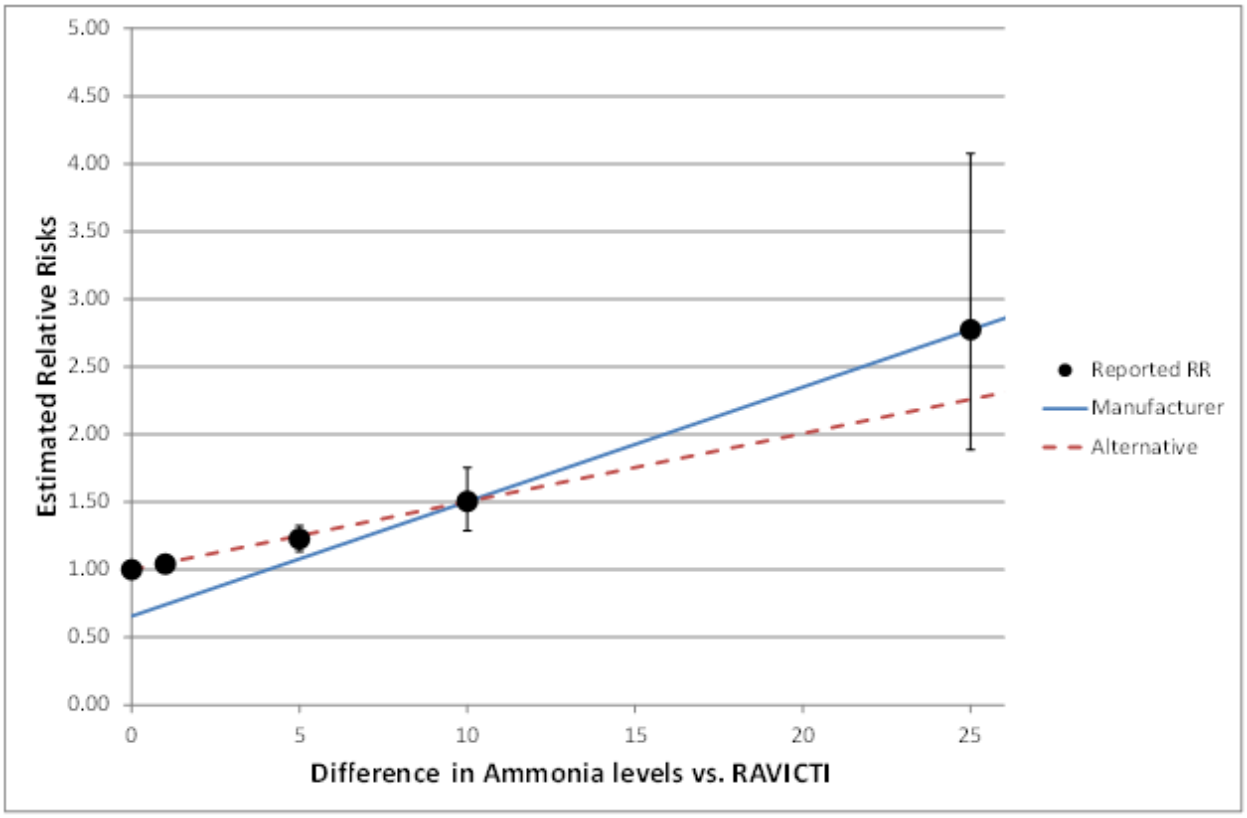
CDR = CADTH Common Drug Review; DC = dietary control plus supplementation only; GPB = glycerol phenylbutyrate; ICUR = incremental cost-utility ratio; NaPBA = sodium phenylbutyrate; QALY = quality-adjusted life-year; vs. = versus.

APPENDIX 4: CLINICAL DATA USED IN REANALYSIS

The manufacturer's calculated relative risk for hyperammonemic crisis (HAC) appears to be a potential key driver of results, especially within the model in Subgroup 2 and Subgroup 4, in which dietary control is considered as the comparator for glycerol phenylbutyrate (GPB). As outlined in the preceding sections, the estimates for the relative risk of HAC are based on an extrapolation of already estimated points. Any linear interpolation of this type is inherently risky, as the relationships that underlie data within a given range do not necessarily determine the data over other ranges. In particular, the studies appear to compare the incidence of HACs in periods when patients receive GPB and periods when they receive sodium phenylbutyrate (NaPBA).

To illustrate the difficulty with using linear interpolation in this way, we present three diagrams. Figure 2 displays the reported relative risks for differences in ammonia levels versus GPB outcomes. These data are presented in the manufacturer's submission Table 3, with error bars displaying the confidence intervals for each data point. The manufacturer proposes using a linear interpolation between the data points at a difference of 10 and a difference of 25. When plotted, it is noticeable that this relationship does not explain the points at differences of one and five very well at all. (There is an additional point at zero; trivially, if there is no difference, we would expect a relative risk of HACs of one.)

FIGURE 2: MANUFACTURER'S REPORTED RELATIVE RISKS AND ALTERNATIVE



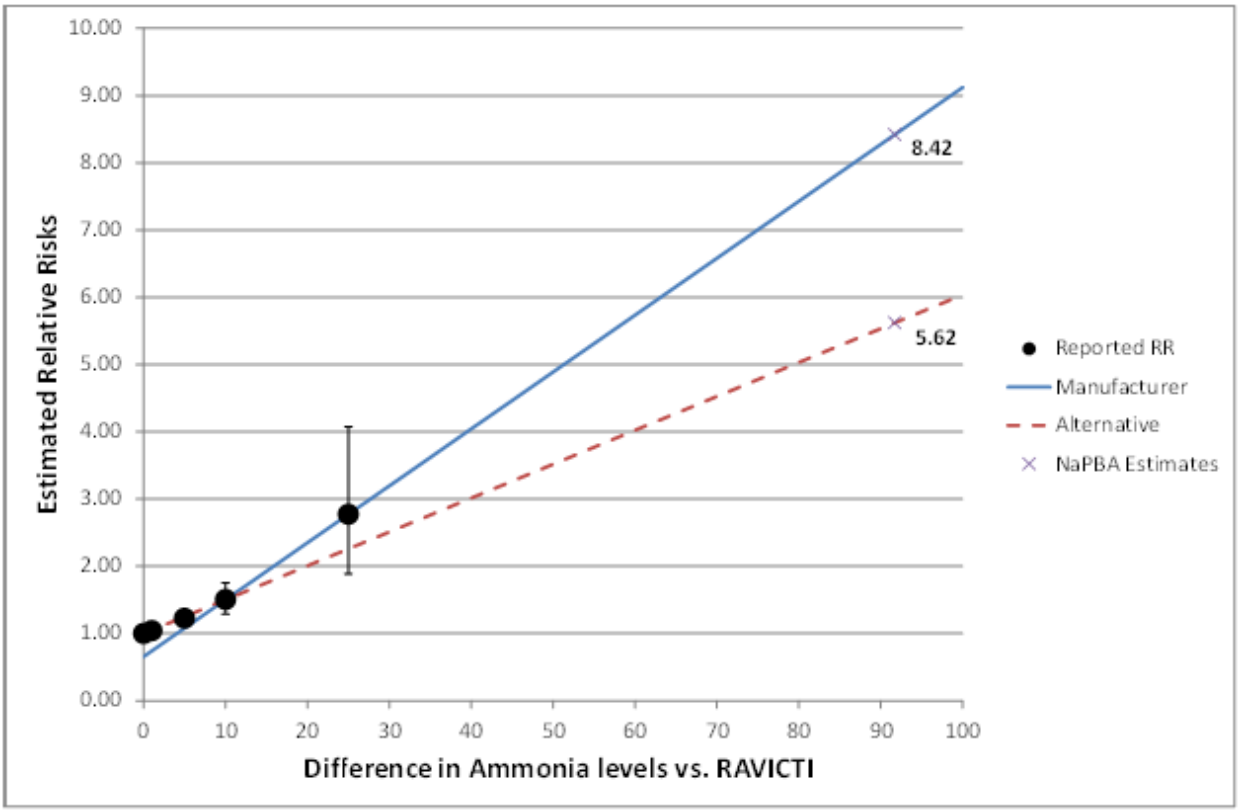
RR = relative risk.

The second fitted curve shows the estimated relationship if there is a linear interpolation between a difference of zero and a difference of 10. This line passes within the confidence intervals for every one of the data points, and provides an arguably more robust fit.

Figure 3 shows these curves extended to allow them to explain points outside the range of the data. At the difference in ammonia levels claimed by the manufacturer for dietary control of 91.7 µmol/L, the difference is between the relative risk of 8.42 claimed by the manufacturer and relative risk of 5.62 in the alternative extrapolation. This establishes that, if using these points, there may be significant uncertainty about which point to use.

Although the manufacturer uses linear interpolation, this is not consistent with the analysis that underlies the data presented (including the error bars, etc.). That is, the analysis *determines* the relationship between the two variables, and defines how this should be approached in any interpretation of that analysis.

FIGURE 3: MANUFACTURER'S REPORTED RELATIVE RISKS AND ALTERNATIVE, EXTRAPOLATED

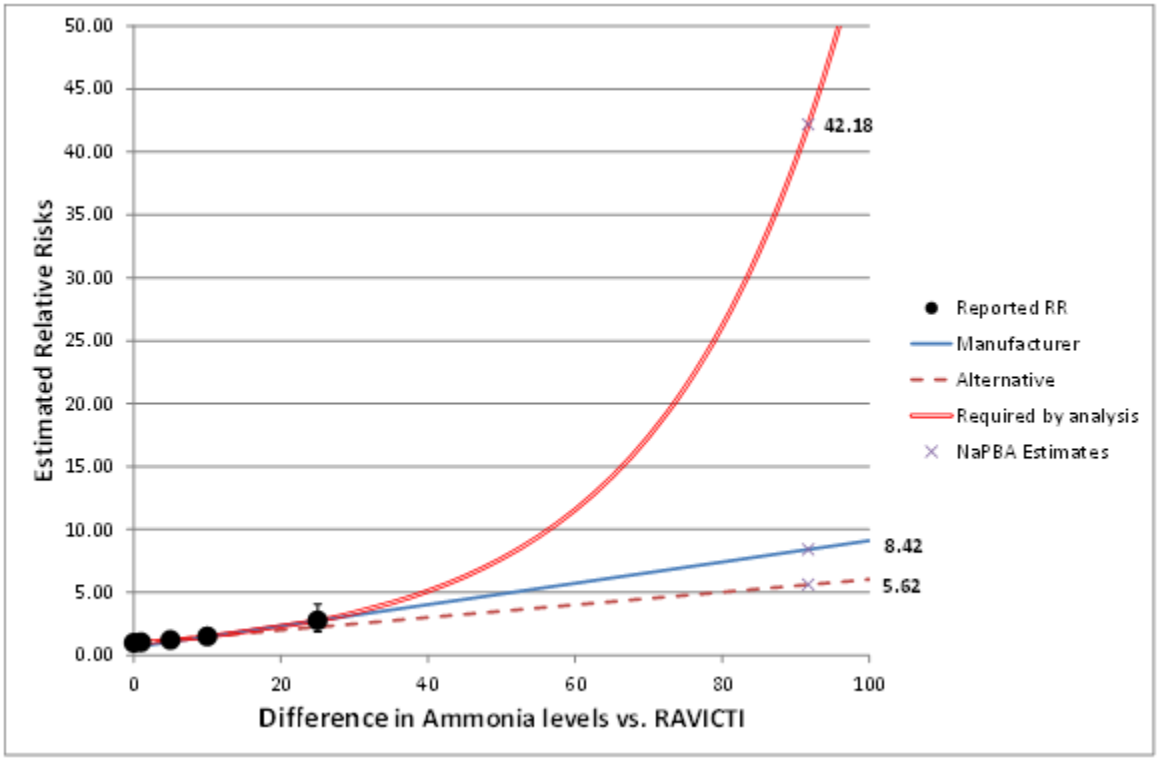


NaPBA = sodium phenylbutyrate; RR = relative risk.

In this case, the analysis appears to fit a linear relationship between log-relative risk and difference in ammonia levels. Since this estimated relationship can be extracted, the estimates based on this analysis are available and shown in Figure 4.

However, this leads to a relative risk of 42.18. As the GPB analysis uses an average of 0.27 HACs per patient, per year, this suggests 11.4 HACs per year under dietary control, so that those on dietary control are assumed to have HACs nearly every month if using this analysis.

FIGURE 4: RELATIVE RISK INFERRED USING PRIOR ANALYSIS, VERSUS PRIOR ESTIMATES



Revised Results Based on Reconstructed Model (CDR Baseline)

A safer approach may be to use the data available. The manufacturer uses an observational study of patients receiving Pheburane,[3] which reports data for 25 patients who had been unable to tolerate Buphenyl. That is, in the previous six months they either were unable to use Buphenyl (so used dietary control only) or used it but had extreme difficulty tolerating it. (The degree to which this really represents a "dietary control" group is unclear.) The manufacturer uses ammonia levels measured in this study, although the more relevant data are likely to be the historic number of HACs in the six months before the study. In the 25 patients enrolled, there were a total of 22 HACs. As there were 25 patients over six months, there were a total of 150 patient-months. HACs occurred in 22 of these patient-months, and did not occur in the remaining 128 months. Expressed as a probability, the parameter representing the monthly risk of HACs under dietary control can be conservatively modelled as coming from the distribution beta (22, 128), since some patients were still receiving NaPBA (poorly tolerated Buphenyl).

Likewise, Lee et al. 2015[4] provides data for the GPB and Pheburane groups. For the former, there were 27 HACs over 12 years among 100 patients (1,200 patient-months), yielding 0.27 HACs per year. For the latter, it was reported that there had been 54 HACs in the year before GPB treatment (on Pheburate), for a frequency of 0.54 HACs per year. The probabilities of HACs occurring under GPB and NaPBA can be computed in a similar fashion as with dietary control, leading to distributions beta (27, 1173) and beta (54, 1146), respectively.

Using this data directly allows us to avoid using the estimated relationship between ammonia levels and HAC rates. The short-term GPB trials are not used but, instead, the three longer-term studies and/or extensions are used (HPN-100-007, HPN-100-005 safety extension, HPN-100-012 safety extension). However, the methodological quality of this data is poor as these studies are uncontrolled (in the case of the 60 patients in HPN-100-007) or open-label (in the case of the 40 patients across the two safety extension studies).

REFERENCES

1. [Pr]Ravicti™ (glycerol phenylbutyrate): oral liquid, 1.1 g/mL [product monograph]. Dublin: Horizon Pharma Ireland Ltd.; 2016 Mar 16.
2. Pharmacoeconomic evaluation. In: CDR submission: Ravicti™, glycerol phenylbutyrate, 1.1 g/mL, oral liquid. Company: Horizon Therapeutics Canada [**CONFIDENTIAL** manufacturer's submission]. Ottawa (ON): Horizon Therapeutics Canada; 2016 Aug 29.
3. Kibleur Y, Dobbelaere D, Barth M, Brassier A, Guffon N. Results from a nationwide cohort temporary utilization authorization (ATU) survey of patients in France treated with Pheburane((R)) (sodium phenylbutyrate) taste-masked granules. Paediatr Drugs. 2014 Oct;16(5):407-15.
4. Lee B, Diaz GA, Rhead W, Lichter-Konecki U, Feigenbaum A, Berry SA, et al. Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. Genet Med. 2015 Jul;17(7):561-8.
5. Shchelochkov OA, Lee BH, Scharschmidt BF, Dickinson KA, Herberich E, Hawkins S, et al. Assessment of barriers to drug adherence in the treatment of urea cycle disorders in North America. Clin Biochem. 2016;47(15):153.
6. Tanuseputro P, Wodchis WP, Fowler R, Walker P, Bai YQ, Bronskill SE, et al. The health care cost of dying: a population-based retrospective cohort study of the last year of life in Ontario, Canada. PLoS ONE. 2015;10(3):e0121759.