Common Drug Review
Pharmacoeconomic Review Report

April 2016

Drug	Sodium phenylbutyrate (Pheburane)
Indication	As adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinate synthetase, in patients with neonatal-onset presentation and patients with late-onset disease with a history of hyperammonemic encephalopathy.
Listing Request	As per indication
Dosage Form(s)	Coated granules for oral intake
NOC Date	January 26, 2015
Manufacturer	Médunik Canada

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
ASS	argininosuccinate synthetase
BSA	body surface area
CCA	cost-consequence analysis
CDR	CADTH Common Drug Review
CPSI	carbamoyl phosphate synthetase I
NaPB	sodium phenylbutyrate
OTC	ornithine transcarbamylase
PAG	phenylacetylglutamine
PYE	person-years of exposure
SAP	Special Access Programme
RAMQ	Régie de l'assurance maladie du Québec
UCD	urea cycle disorder

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Sodium phenylbutyrate (Pheburane)
Study Question	"What are the anticipated costs and consequences of the use of [NaPB] (Pheburane) for the treatment of UCDs, from a health ministry perspective, compared with the current standard of care?"
Type of Economic Evaluation	CCA
Target Population	Patients with neonatal-onset presentation of UCDs involving deficiencies of CPSI, OTC, or ASS, presenting within the first 28 days of life. It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonemic encephalopathy.
Treatment	Pheburane + standard of care (dietary protein restriction + essential amino acid supplementation)
Outcome(s)	Total life-years Total life-years with neurological impairment
Comparators	NaPB (Buphenyl) + standard of care Glycerol phenylbutyrate (Ravicti) + standard of care
Perspective	Health ministry
Time Horizon	25 years
Results for Base Case	Estimated annual costs[a] (incremental vs. Pheburane) to treat a neonate patient with UCDs: • Pheburane = $44,011 • Buphenyl = $48,864 (+$4,853) • Ravicti = $136,911 (+$92,900) Estimated annual costs[a] to treat a 30-day-old patient with UCDs: • Pheburane = $49,418 • Buphenyl = $54,863 (+$5,445) • Ravicti = $153,567 (+$104,149) Estimated annual costs[a] to treat a 2-year-old patient with UCDs: • Pheburane = $55,000 • Buphenyl = $61,096 (+$6,096) • Ravicti = $171,538 (+$116,538) Estimated life-years (total and with NI) over 25 years with Pheburane, Buphenyl, and Ravicti: • Neonate patients: 12.45 life-years (4.84 life-years with NI) • Patients aged 30 days: 13.88 life-years (3.13 life-years with NI) • Patients aged 2 years: 13.98 life-years (2.71 life-years with NI)

Key Limitations	• Based on the assumption of equal efficacy and safety of treatments, the manufacturer compared drug costs of interventions — cost-minimization analysis rather than CCA. • Equal effectiveness was assumed based on the bioequivalence of Pheburane and Buphenyl; and although Ravicti is currently being reviewed by Health Canada, the manufacturer assumed equivalent clinical effectiveness versus others based on results of non-inferiority trials that were not provided by the manufacturer. This assumption of equal safety and efficacy is not fully supported. • The manufacturer did not consider standard of care alone (referred to as the combination of dietary protein restriction and essential amino acid supplementation). This may limit decision-making in jurisdictions, as Buphenyl may no longer be accessible and Ravicti is not available in Canada. • Cost of Ravicti was obtained from US sources. Because Ravicti is not yet marketed in Canada, it is unclear how Pheburane will compare against Ravicti if introduced to Canada. • Inappropriateness of the efficacy study used for modelling due to issues identified with study design and included treatment. • Model structure and assumptions limited the exploration of uncertainty of treatment effects on model outcomes.
CDR Estimate(s)	• Due to scarcity of data and model limitations, CDR was unable to conduct reanalyses to address the aforementioned limitations. • CDR validated the costs reported by the manufacturer, even after correcting issues with the model.

ASS = argininosuccinate synthetase; CCA = cost-consequence analysis; CDR = CADTH Common Drug Review; CPSI = carbamoyl phosphate synthetase; NaPB = sodium phenylbutyrate; NI = neurological impairment; OTC = ornithine transcarbamylase; UCD = urea cycle disorder; vs. = versus.

[a] Average annual drug cost over a 25-year time horizon (discounted). Considers treatment cost, hospitalization cost, health care professional contact cost, and background pharmaceutical therapy cost. Only the primary treatment drug costs (Pheburane, Buphenyl, and Ravicti) vary between compared treatment arms because of the method used for the economic analysis.

EXECUTIVE SUMMARY

Background

Pheburane is a tasteless, coated granule formulation of sodium phenylbutyrate (NaPB) that is converted in the gut to sodium phenylacetate (NaPA), which is conjugated in the liver with glutamine to form phenylacetylglutamine (PAG), which is in turn excreted by the kidneys. Other commercial formulations of NaPB in Canada include Buphenyl, which had been previously available through a Health Canada Special Access Programme (SAP). Pheburane is indicated as adjunctive therapy in the chronic management of urea cycle disorders (UCDs), involving deficiencies of carbamoyl phosphate synthetase I (CPSI), ornithine transcarbamylase (OTC), or argininosuccinate synthetase (ASS). Pheburane is indicated for patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life) and in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonemic encephalopathy.[1] The recommended dosing for Pheburane is as follows:

- 450 to 600 mg/kg/day in neonates, infants, and children weighing less than 20 kg
- 9.9 to 13.0 g/m^2/day in children weighing more than 20 kg, adolescents, and adults.

The manufacturer submitted a price of $0.01919 per mg,[2] which corresponded to an annual cost of approximately:

- $10,401 to $75,647 for patients weighing less than 20 kg.
- $56,237 to $157,678 for patients weighing more than 20 kg.

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

A cost-consequence analysis (CCA) was submitted comparing Pheburane (NaPB) to Buphenyl (NaPB) and Ravicti (glycerol phenylbutyrate) based on the bioequivalence of Pheburane and Buphenyl and with the assumption of equivalent clinical effectiveness.[2] Although Ravicti is currently being reviewed by Health Canada, the manufacturer assumed equivalent clinical effectiveness between Ravicti and NaPB formulations based on results of non-inferiority trials that were not provided by the manufacturer in this submission. The effects of NaPBs and Ravicti on hyperammonemia were based on survival and hospitalization information reported in a 25-year study published in 2007 of intravenous Ammonul (NaPB and sodium benzoate) for in-patient treatment of acute hyperammonemic episodes.[2,3] The analysis time horizon was 25 years, conducted from the Canadian health ministry perspective. Standard of care (SOC) was not assessed as a comparator.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several limitations with the submitted analysis. The analysis was submitted as a CCA but was based on the assumption of equal safety and efficacy between the drug comparators based on bioequivalence data and results from an unavailable non-inferiority trial — therefore, it was effectively a cost-minimization analysis. The submitted analysis did not consider SOC as a comparator and the model did not allow for the assessment of the comparative effectiveness of Pheburane versus SOC alone. The submitted analysis considered only the drug comparators Buphenyl and Ravicti. This limits decision-making in jurisdictions, as Buphenyl may no longer be accessible through SAP now that Pheburane has been made commercially available in Canada, and Ravicti is not commercially available in Canada.

In addition to the fact that the CCA did not report results in disaggregate form for either costs or health outcomes for the assessed treatments, other major limitations are the inappropriateness of the effectiveness data used to populate the CCA, the underestimation of hospitalization costs, and the underestimation of mortality due to hyperammonemic events. However, varying the three latter limitations would not affect the comparative assessment of the three compared drugs, as the model was based on the assumption of equality between arms for all these effectiveness components with very limited capabilities to exploring uncertainty of treatment effect parameters on model outcomes.

Due to scarcity of data and the model limitations, CDR was unable to conduct reanalyses to address the aforementioned limitations.

Because Ravicti is not yet marketed in Canada, it is unclear if its expected price will be similar or different to that used in the analysis.

Conclusions

There are a number of limitations with the submitted analysis, including mainly the type of submitted economic evaluation; the omission of SOC alone as a comparator; the uncertainty with the assumption of equal safety and efficacy, especially for Pheburane versus Ravicti; and the lack of presented comparative clinical evidence for Pheburane versus Buphenyl and versus Ravicti as adjunctive therapy in the chronic management of UCDs.

Based on the manufacturer's assumptions of equal safety and efficacy, Pheburane is expected to cost between $35,674 and $54,752 per patient per year and is expected to lead to cost savings compared with Buphenyl (savings between $3,913 and $6,061 per patient per year). Because Ravicti is not yet marketed in Canada, its price was obtained from US sources; it is unclear how Pheburane will compare against Ravicti if introduced to Canada.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-consequence analysis (CCA) presenting the anticipated costs and clinical outcomes associated with Pheburane (sodium phenylbutyrate [NaPB]) compared with Buphenyl (NaPB) and with Ravicti (glycerol phenylbutyrate) as adjunctive therapy in the chronic management of urea cycle disorders (UCDs). By definition, CCAs present a detailed listing of the various impacts on outcomes associated with intervention under review, with no attempt to value the aggregated components in a single metric.[4] The manufacturer submitted a model utilizing a 5-state design (Figure 1), using one-month cycle length over a 25-year time horizon to estimate the incremental costs of Pheburane compared with Buphenyl and with Ravicti and to report on the health outcomes expected from the treatment strategies.[2] The compared treatment arms in the model (i.e., Pheburane, Buphenyl, and Ravicti) relied on survival and hospitalization information reported in a 25-year study of Ammonul for the in-patient treatment of acute hyperammonemic episodes, published by Enns et al. (2007),[3] that reported the outcomes with patients in multiple age groups, and treated using extensive therapy. Data from Enns et al.[3] were used for compared treatment arms assuming equal safety and efficacy between these.

Drug acquisition costs were based on the cost per milligram of active ingredient, multiplied by the dose per kilogram of patient weight.[2] Patient weights were calculated on the basis of reported population norms[5] and the recommended dose of each drug was then multiplied by the appropriate weights of body surface area (BSA). Costs accrued in the remission health states are limited to the cost of background therapies, contacts with health care specialists every three months, and acquisition costs for the primary nitrogen scavenger. In the event health states, costs include hospitalization, drug acquisition cost, and background therapy cost. Transition probabilities for all arms of the model were based on rates reported in Enns et al. (2007).[2,3] Background risk of death was modelled in every health state based on life tables obtained from Statistics Canada.[2]

2. MANUFACTURER'S BASE CASE

The results of the manufacturer's base case showed that Pheburane was the least costly compared with Buphenyl and Ravicti irrespective of the starting age (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE OVER 25 YEARS

Treatment	Starting Age	Total Costs	Life-Years (Total)	Life-Years (Neurological Impairment)
Pheburane	Neonate	$1,100,269	12.45	4.84
Buphenyl	Neonate	$1,221,602	12.45	4.84
Ravicti	Neonate	$3,422,781	12.45	4.84
Pheburane	30 days	$1,235,456	13.88	3.13
Buphenyl	30 days	$1,371,578	13.88	3.13
Ravicti	30 days	$3,839,162	13.88	3.13

Treatment	Starting Age	Total Costs	Life-Years (Total)	Life-Years (Neurological Impairment)
Pheburane	2 years	$1,375,011	13.98	2.71
Buphenyl	2 years	$1,527,389	13.98	2.71
Ravicti	2 years	$4,288,440	13.98	2.71

Source: Manufacturer's pharmacoeconomic submission, Table 5.1a (page 29).[2]

2.1 Summary of Manufacturer's Sensitivity Analyses

The manufacturer indicated that variability was not explicitly considered in the submitted model and neither was heterogeneity, based on the lack of available data to inform the impact of different disease etiologies on different disease severities with UCD. There was uncertainty regarding the parameter values, which were tested using scenario and univariate deterministic sensitivity analyses. Scenario analyses varied the time horizon to 10 and 50 years (base case 25 years), discount rate values to 0% and 3% (base case 5%), and examined the assumption that the costs of hospitalization are constant over time by assigning a rising or declining cost of hospitalization with a rate of 2% per year from the end of year 1 to the end of the model time horizon. Univariate sensitivity analyses were performed on several parameters in the model. Results of all the scenario and sensitivity analyses indicated the robustness of the results of the base-case analysis.

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

3.1 Type of Evaluation

The manufacturer conducted a CCA with the aim of providing the decision-maker with the expected costs and resource use, as well as health outcomes, associated with the use of Pheburane. The model submitted as part of the CCA was based on a primary assumption of equal efficacy and safety between the compared interventions — Pheburane, Buphenyl, and Ravicti — based on bioequivalence data. Therefore, the comparators will be expected to produce similar health outcomes but at different drug costs. This primary assumption effectively rendered the submitted analysis a cost-minimization analysis that only compares treatments in terms of costs and not health outcomes. A submission based on a cost-minimization analysis would have been more appropriate.

3.2 Comparative Effectiveness of Pheburane as Adjunctive Therapy to Standard Care Versus Standard Care Alone is not Modelled

The manufacturer's CCA analysis did not include a comparator arm of standard care alone (referred to as the combination of dietary protein restriction and essential amino acid supplementation) despite the CCA mentioning four comparator arms but only reporting on three arms (Pheburane, Buphenyl, and Ravicti). The SOC comparator may be useful for decision-making in some jurisdictions, as Buphenyl may no longer be accessible through the Special Access Programme (SAP) now that only Pheburane is commercially available in Canada, while Ravicti remained under review by Health Canada at the time of this review.

3.3 Results of the Cost-Consequence Analysis

The aim of conducting a CCA is to present the disaggregated costs and clinical outcomes associated with the use of Pheburane compared with NaPB treatments in patients with UCDs. The CCA provided by the manufacturer limited the reported costs of each comparator arm to drug acquisition costs and total hospitalization costs; it was unclear what resources and costs were included under the hospitalization

costs. The submitted analysis also included an assumption that all neurological impairments were to be grouped rather than reported in disaggregate form; it would therefore have been unclear how Pheburane could have affected the incidence of various neurological impairments (e.g., cerebral palsy, seizure disorders, psychiatric disorders, blindness, etc.). However, because the manufacturer's CCA was based on the assumption of equal efficacy between comparators, the results of the CCA were not expected to show any changes in terms of outcomes between the comparators. Therefore, the reporting of the CCA's clinical outcomes appears to be unnecessary.

3.4 Appropriateness of Efficacy Study by Enns et al. (2007)[3] to Inform CCA

The manufacturer's CCA relied primarily on the 25-year publication by Enns et al. (2007)[3] to inform several parameters of the submitted model: natural history of the disease, efficacy of compared treatments in UCD, transition probabilities between model health states, acute event rates, and death rates during a hyperammonemic event. Issues identified with the study raised uncertainty over the appropriateness of using the Enns publication to inform the model: the study investigated a different product, which was administered intravenously in hospital (Ammonul), and which is indicated for the treatment of acute hyperammonemia while Pheburane is an oral product that is indicated for chronic management of UCDs.[1] The clinical expert indicated that Pheburane is not considered a rescue medication for UCD in clinical practice and that rescues doses of Ammonul, as used in the Enns study, were considered to be double the expected dosage for Pheburane. Therefore, use of efficacy data for Ammonul to inform that of other drugs warrants cautious consideration.

3.5 Hospitalization Costs

The cost per hospitalization used by the manufacturer in the CCA analysis was approximately $8,503; this value was considered to be significantly low by the clinical expert who suggested, quoting unpublished data, that the average cost for a UCD patient is closer to $1 million dollars, which includes scavengers, diet restriction, and three to four hospitalizations per year. Although such estimates could not be verified, and based on the manufacturer's assumption of equal efficacy between comparators, the impact of hospitalization costs is not expected to differ between comparators.

3.6 Mortality Due to a Hyperammonemic

The manufacturer had made the assumption in the base case of the model that 10.38% of patients will not survive the index hyperammonemic episode when treated with compared treatments. No information was provided as to how this value was estimated or obtained. The clinical expert mentioned that in clinical practice, it is very likely that the number of patients on compared treatment who will not survive a hyperammonemic event is much higher than the assumed 10.38%.

3.7 Cost of Ravicti

The manufacturer applied the cost of Ravicti from US sources into the Canadian CCA. Because Ravicti is currently under review by Health Canada, it is not clear whether its expected list price in Canada will be similar to or different from that of the US cost used by the manufacturer.

3.8 Model Limitations

As previously noted, the analysis was based on the assumption of equal efficacy and safety between the included comparator drugs. This assumption was also represented in the design and structure of the submitted model, which limits exploratory analyses regarding the uncertainty of the treatment effects on the model outcomes.

3.9 CADTH Common Drug Review Reanalyses

CDR identified limitations with the manufacturer's CCA, mainly that the assumption of clinical equivalence between treatments in event rates from a study of an in-patient acute treatment are representative of the target patient population. Due to scarcity of data, CDR was unable to conduct reanalyses to address the aforementioned limitations.

However, CDR did rerun the analyses presented by the manufacturer, correcting some issues with the model. The results of the CDR analyses in Table 3 are aligned with the base-case results provided by the manufacturer.

TABLE 3: SUMMARY OF RESULTS OF CADTH COMMON DRUG REVIEW REANALYSES FOR PHEBURANE OVER 25-YEAR TIME HORIZON

Treatment	Starting Age	Costs	Incremental Costs (Compared With Pheburane)	Incremental (per Patient per Year)
Pheburane	Neonate	$891,850	-	-
Buphenyl	Neonate	$989,676	$97,826	$3,913
Ravicti	Neonate	$2,764,332	$1,872,482	$74,899
Pheburane	30 days	$1,230,641	-	-
Buphenyl	30 days	$1,366,072	$135,431	$5,417
Ravicti	30 days	$3,820,899	$2,590,258	$103,610
Pheburane	2 years	$1,368,798	-	-
Buphenyl	2 years	$1,520,324	$151,526	$6,061
Ravicti	2 years	$4,265,624	$2,896,826	$115,873

4. ISSUES FOR CONSIDERATION

According to the clinical expert, there is potential for off-label use of Pheburane as an alternative for the more expensive carglumic acid (Carbaglu [carglumic acid] was issued a Notice of Compliance by Health Canada on April 10th 2015[6]) for the treatment of hyperammonemia due to other reasons such as herpes infection. Treatment might resolve herpes, but because hyperammonemia is still an issue, the use of scavenger proteins (e.g., Pheburane, Buphenyl, and Ravicti) would be considered an attractive option. In addition, the product monograph for Pheburane does not include a contraindication to the use of Pheburane as an alternate for carglumic acid in lyase-deficient patients.

4.1 Patient Input

Input was received from one patient group, the National Urea Cycle Disorders Foundation. The submission noted that Pheburane's improved administration profile and taste-masked formulation are expected to improve compliance with the drug, optimize control of the disorder, and improve the lives of patients and their caregivers. The submission noted that Pheburane is expected to involve fewer hospital visits, reduce burden on caregivers, and include less time off work. The manufacturer's model was from the perspective of the ministry of health; therefore, indirect costs and resource use such as caregiver burden and time off work were not included. The model's results did not associate the administration of Pheburane to any reduction in hospital visits compared with Buphenyl or Ravicti.

5. CONCLUSIONS

There are a number of limitations with the submitted analysis, including the type of submitted economic evaluation; the omission of SOC alone as a comparator; the uncertainty regarding the assumption of equal safety and efficacy, especially for Pheburane versus Ravicti; and the lack of presented comparative clinical evidence for Pheburane versus Buphenyl and versus Ravicti as adjunctive therapy in the chronic management of UCDs.

Based on the manufacturer's assumptions of equal safety and efficacy, Pheburane is expected to cost between $35,674 and $54,752 per patient per year and is expected to lead to cost savings compared with Buphenyl (savings between $3,913 and $6,061 per patient per year). Because Ravicti is not yet marketed in Canada, its price was obtained from US sources; it is unclear how Pheburane will compare against Ravicti if introduced to Canada.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 4 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON TABLE

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Sodium phenylbutyrate (Pheburane)	483 mg per gram of granules	Granule	0.01919[a]/mg	Patient weight < 20 kg: 450 to 600 mg/kg/day Patient weight ≥ 20 kg: 9.9 to 13.0 g/m^2/day Max dose of 20 g/day	$28.50 to $207.25 $154.07 to $431.99 $383.80	$10,401 to $75,647 $56,237 to $157,678 $140,087
Nitrogen-binding agents						
Sodium phenylbutyrate (Buphenyl)	500 mg	Tab powder	0.02140[b]/mg	Patients weight > 20 kg: 450 to 600 mg/kg/day Patient weight ≥ 20 kg: 9.9 to 13.0 g/m^2/day Max dose of 20 g/day	$31.78 to $231.12 $171.82 to $481.75 $428.00	$11,599 to $84.359 $62,713 to $175,837 $156,220
Glycerol phenylbutyrate (Ravicti)	1.1 g/mL	Oral liquid	0.107[a]/mg	4.5 to 11.2 mL/m^2/day (5 to 12.4 g/m^2/day) in 3 equally divided doses, rounded up to the nearest 0.5 mL Max daily dose of 17.5 mL (19 g)	$470.80 to $2,295.15	$171,842 to $837,730
Carboxylic acid and derivatives						
Carbaglu (carglumic acid)	200 mg[c]	Tablets	Price information not available	Initial dose should be 100 mg/kg/day, up to 250 mg/kg/day Maintenance doses range from 10 mg/kg/day to 100 mg/kg/day	Price information not available	Price information not available

[a] Manufacturer's submission.[2]

[b] Quebec Drug Formulary based on manufacturer's submission.[2]

[c] Carbaglu (carglumic acid) was issued a Notice of Compliance by Health Canada on April 10th 2015.[6]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS PHEBURANE RELATIVE TO BUPHENYL?

Pheburane Versus Buphenyl	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes						X
Quality of life						X
Incremental CE ratio or net benefit calculation	NA					

CE = cost-effectiveness; NA = not applicable.

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS PHEBURANE RELATIVE TO RAVICTI?

Pheburane Versus Ravicti	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes						X
Quality of life						X
Incremental CE ratio or net benefit calculation	N/A					

CE = cost-effectiveness; NA = not applicable.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments			
Was the material included (content) sufficient?		X	
Comments			
Was the submission well organized and was information easy to locate?		X	
Comments			

TABLE 8: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the 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): Original analysis done by private consultant contracted by the manufacturer			
	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 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

The Scottish Medicines Consortium (SMC) had completed its assessment of Pheburane and issued an advice in October 2013, recommending the use of Pheburane within Scotland as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamoyl phosphate synthetase, ornithine transcarbamylase, or argininosuccinate synthetase.[7] The published advice did not provide details on the submitted economic analysis for Pheburane. However, the advice did conclude by stating that Pheburane granules provide an alternative to sodium phenylbutyrate tablets at no additional cost, but are more expensive than an existing brand of sodium phenylbutyrate granules.[7]

The All Wales Medicines Strategy Group (AWMSG) issued a recommendation in November 2013 for Pheburane as an option for use within Wales for the same indication.[8] The manufacturer had submitted a budget impact analysis that included a comparison of the annual costs associated with the use of Pheburane compared with Ammonaps (sodium phenylbutyrate) for the treatment of urea cycle disorders. The manufacturer had estimated that approximately five out of a total of nine patients in Wales would be eligible for treatment with Pheburane; however, the manufacturer had not provided evidence to support this number.[8]

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-consequence analysis (CCA) presenting the anticipated costs and clinical outcomes associated with sodium phenylbutyrate as adjunctive therapy in the chronic management of urea cycle disorders (UCDs). By definition, CCAs present a detailed listing of the various impacts on outcomes associated with intervention under review, with no attempt to value the aggregated components in a single metric.[4] The manufacturer submitted a Markov model utilizing a five-state design (Figure 1), using one-month cycle length over a 25-year time horizon to estimate the incremental costs of adoption of Pheburane compared with Buphenyl and with Ravicti, and to report on the health outcomes expected from the treatment strategies.[2]

The remission health states (i.e., either neuro-normal or neuro-impaired) represent cycles wherein patients are free from acute hyperammonemic episodes. The event health states refer to acute hyperammonemic episodes resulting in hospitalization. The "neuro-impaired" states represent tunnel states, allowing the disaggregation of survival with and without neurological impairment in the results. Death constitutes an absorbing state within the model, and no transition from this state is possible. The manufacturer assumed that patients in the neonatal model started in the event neuro-normal state, while patients in the other cohorts began in remission neuro-normal. This was based on the expectation that neonatal presentation is characterized by active hyperammonemia.

The compared treatment arms in the model (i.e., Pheburane, Buphenyl, and Ravicti) relied on survival and hospitalization information reported in a 25-year study of Ammonul for the in-patient treatment of acute hyperammonemic episodes, published by Enns et al. (2007),[3] that reported the outcomes with patients in multiple age groups and treated using extensive therapy. Although the use of Ammonul is for in-patient treatment for acute care, the manufacturer assumed that maintenance therapy throughout the study was considered comparable with Pheburane-, Buphenyl-, and Ravicti-assessed treatment arms.

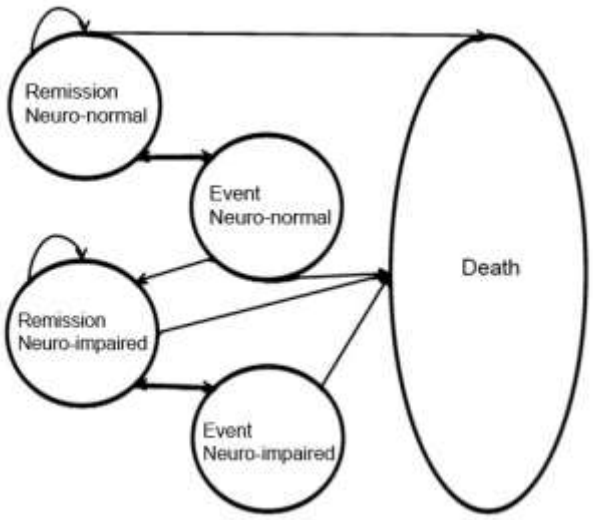
Drug acquisition costs were based on the cost per milligram of active ingredient, multiplied by the dose per kilogram of patient weight.[2] Patient weights were calculated on the basis of reported population norms[5] and the recommended dose of each drug was then multiplied by the appropriate weights of body surface area (BSA). These norms were then used to calculate the expected dose per cycle in a time-dependent manner (i.e., patients grew at the rate of time advancement in the model, and so the dose continued to increase until patient weight reached a plateau). The same approach was used for the calculation of dosing and costs for background therapies. Costs accrued in the remission health states are limited to the cost of background therapies, contacts with health care specialists every three months, and acquisition costs for the primary nitrogen scavenger. In the event health states, costs include hospitalization, drug acquisition cost, and background therapy cost. The manufacturer assumed that each state other than death accrued one-twelfth of a life-year as a pay-off.

Transition probabilities for all arms (assuming equality) of the model were based on rates reported in Enns et al. (2007).[2,3] The transition probabilities were reported in a series of age groups, including neonatal patients, age 30 days to two years, two years to 12 years, and older than 12 years. The manufacturer assumed that the events rates are reflective of the anticipated outcomes for these age groups, regardless of previous medical history; i.e., at what age diagnosis or first event occurred. Transitions probabilities include transition from remission to hyperammonemic event, and for every

state to death. The transition probabilities were time dependent, because the Enns et al. (2007) publication reported different event rates at different ages.[2,3] Background risk of death was modelled in every health state based on life tables obtained from Statistics Canada.[2]

Validation of the model results included a comparison of survival and event rates predicted by the model with those reported elsewhere: model survival results were compared with those reported by Kido et al. (2012),[9] and hyperammonemic event rates were compared with those reported in Maestri et al. (1996).[10]

FIGURE 1: SCHEMATIC OVERVIEW OF PHARMACOECONOMIC MODEL FOR SODIUM PHENYLBUTYRATE IN UREA CYCLE DISORDERS



Source: Manufacturer's Pharmacoeconomic submission.[2]

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	The efficacy of sodium phenylbutyrate (Pheburane and Buphenyl) and glycerol phenylbutyrate (Ravicti) is based on a 25-year study of Ammonul (sodium phenylacetate and sodium benzoate injection) in-patient treatment of acute hyperammonemic episodes (Enns et al. 2007).[3] The equality in effect of Pheburane and Ravicti was based on non-inferiority studies; however, these studies were not provided by the manufacturer in this submission. Because standard of care was not included as a comparator in the analysis, no comparative evidence versus Pheburane was provided.	Inappropriate. Pheburane is an oral product indicated as adjunctive treatment for the chronic management of hyperammonemia, while Ammonul is indicated for acute cases (i.e., rescue drug) and is administered intravenously. The clinical expert on this review expressed concern over the outdatedness of the Enns publication and its use for the review of Pheburane.

Data Input	Description of Data Source	Comment
Natural history	Based on the Enns et al. (2007)[3] publication, which reported rates in a series of age groups, including neonatal patients, age 30 days to 2 years, 2 years to 12 years, and older than 12 years.	Concerns were expressed by the clinical expert regarding the use of this study in the context of the submission.
Mortality	Probability of death due to a hyperammonemic event was obtained from rates reported in the Enns et al. (2007)[3] study after the index episode. The value of the index episode is based on Kido (2012),[9] which reported a 5-year survival rate of 86% and a 10-year survival rate of more than 80% in OTC patients. Background risk of death was based on life tables obtained from Statistics Canada. No additional information was provided by the manufacturer.	Likely inappropriate. Based on clinical expert opinion, the suitability of the Enns study of an acute care treatment to that of Pheburane, a treatment for chronic management, is questionable.
Utilities	Not assessed	Appropriate, considering the type of analysis used.
Resource use	Based on the Enns et al. (2007)[3] publication	Concerns were expressed by the clinical expert regarding the use of this study in the context of the submission.
Adverse events	Not assessed	
Costs		
Drug	Drug acquisition costs for Buphenyl and background therapies were obtained from the Quebec drug plan (RAMQ).[2] Drug acquisition costs for Ravicti were obtained from the US. No information was provided about the source.	Unavailable to verify drug acquisition costs used by the manufacturer for Buphenyl, Ravicti, and background therapies.
Event	Hospitalization costs are estimated at $8503.81, based on average costs quoted by RAMQ for the period 2013-2014.[3]	Clinical expert strongly suggested that actual hospitalization costs to treat hyperammonemia were significantly higher than the costs assumed by the manufacturer.

OTC = ornithine transcarbamylase; RAMQ = Régie de l'assurance maladie du Québec.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Pheburane was compared with Buphenyl and Ravicti.	Inappropriate. Standard of care was not included as a comparator, considering that Buphenyl may no longer be accessible through SAP now that Pheburane is commercially available in Canada and Ravicti is currently under review by Health Canada.
Assumption of clinical equivalence between treatments.	This assumption effectively renders the submitted cost-consequence analysis into a cost-minimization analysis.
Buphenyl is included as a comparator with an assumption of equivalent clinical effectiveness based on bioequivalence.	May be appropriate.

Assumption	Comment
Because Ravicti has been assessed in non-inferiority trials comparing it with NaPB with results demonstrating non-inferiority, equivalent clinical effectiveness between Ravicti and the NaPB formulations was assumed.	Likely appropriate, according to the clinical expert. However, no information was provided on the non-inferiority trials.
In the neonate patient population, patients enter the model in the event neuro-normal health states, while patients in other cohorts begin in the remission neuro-normal health state.	Likely appropriate.
Event rates reported by age group in Enns et al. were assumed to be representative of the patient population at each group, regardless of previous medical history.	Inappropriate. According to the manufacturer, the extent to which Enns et al. (2007)[3] is longitudinal was not clear; therefore, the number of patients who were continuously monitored from the earliest age onward was not clear.
Prior experience of hyperammonemic events does not affect the risk of subsequent events.	Uncertain, according to the clinical expert.
Neurological impairments due to hyperammonemic events have been grouped together.	Inappropriate. A cost-consequence analysis should present the disaggregated costs and clinical outcomes associated with expected use of a treatment or intervention.
The hospitalization cost was assumed to remain constant (i.e., no decline or increase over time).	Inappropriate. According to the clinical expert, the costs are expected to change over time, depending on acuteness of hyperammonemic episode and patient age and response to treatment.
Events are assumed to be of equal cost in neurologically normal and neurologically impaired patients.	Likely inappropriate, as patients with neurological impairment are expected to require additional resources and costs than patients without neurological impairment.
In the base case of the model, 10.38% of patients will not survive the index hyperammonemic episode when treated with compared drugs.	Inappropriate. The clinical expert confirmed that the 10.38% was considered an underestimate.

NaPB = sodium phenylbutyrate; SAP = Special Access Programme.

Manufacturer's Results

The base-case results for the three age groups over a 25-year time horizon are available in Table 2. Disaggregated base-case results in terms of costs over the 25-year time horizon are shown in Table 11. Of note, the manufacturer did not model the neurological impairments of hyperammonemic events in disaggregate form; impairments were grouped together.

TABLE 11: SUMMARY OF DISAGGREGATED RESULTS OF THE MANUFACTURER'S BASE CASE OVER 25 YEARS

Treatment	Starting Age	Hospitalization Costs	Primary Drug Acquisition Costs[a]
Pheburane	Neonate	$24,228.60	$1,067,958.20
Buphenyl	Neonate	$24,228.60	$1,189,290.87
Ravicti	Neonate	$24,228.60	$3,390,560.44
Pheburane	30 days	$27,296.19	$1,199,149.23
Buphenyl	30 days	$27,296.19	$1,335,271.17
Ravicti	30 days	$27,296.19	$3,802,855.47
Pheburane	2 years	$24,070.44	$1,341,842.43

Treatment	Starting Age	Hospitalization Costs	Primary Drug Acquisition Costs[a]
Buphenyl	2 years	$24,070.44	$1,494,220.16
Ravicti	2 years	$24,070.44	$4,255,270.87

[a] Acquisition costs do not include the background therapies.
Source: Manufacturer's Pharmacoeconomic Submission, Table 5.1d (page 32).[2]

Manufacturer's Additional Analyses

The manufacturer's report included results of additional base-case analyses using time horizons of 10 and 50 years. As previously mentioned in this report, the manufacturer's model assumed equivalent effectiveness among the comparators, therefore changing the analysis approach from a cost-consequence analysis to a cost-minimization analysis. The results of the 10- and 50- year analyses show Pheburane to be the least costly treatment (Table 12, Table 13).

TABLE 12: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE OVER 10 YEARS

Treatment	Starting Age	Costs	Life-Years (Total)	Life-Years (Neurological Impairment)
Pheburane	Neonate	$425,392	7.02	2.22
Buphenyl	Neonate	$471,580	7.02	2.22
Ravicti	Neonate	$1,272,609	7.02	2.22
Pheburane	30 days	$480,311	7.82	1.04
Buphenyl	30 days	$532,407	7.82	1.04
Ravicti	30 days	$1,434,250	7.82	1.04
Pheburane	2 years	$571,159	7.85	0.81
Buphenyl	2 years	$633,947	7.85	0.81
Ravicti	2 years	$1,725,591	7.85	0.81

Source: Manufacturer's Pharmacoeconomic Submission, Table 5.1b (page 30).[2]

TABLE 13: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE OVER 50 YEARS

Treatment	Starting Age	Costs	Life-Years (Total)	Life-Years (Neurological Impairment)
Pheburane	Neonate	$1,565,700	15.81	6.98
Buphenyl	Neonate	$1,738,879	15.81	6.98
Ravicti	Neonate	$4,906,205	15.81	6.98
Pheburane	30 days	$1,754,508	17.63	5.16
Buphenyl	30 days	$1,948,448	17.63	5.16
Ravicti	30 days	$5,493,385	17.63	5.16
Pheburane	2 years	$1,900,205	17.77	4.68
Buphenyl	2 years	$2,111,086	17.77	4.68
Ravicti	2 years	$5,962,238	17.77	4.68

Source: Manufacturer's Pharmacoeconomic Submission, Table 5.1c (page 31).[2]

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