CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216513Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) NDA
Application Number(s)	NDA 216513
Priority or Standard	Standard
Submit Date(s)	8/13/2021
Received Date(s)	8/13/2021
PDUFA Goal Date	6/13/2022
Division/Office	Division of Rare Diseases and Medical Genetics (DRDMG/ORPURM/OND)
Review Completion Date	See electronic stamp date
Established/Proper Name	Sodium phenylbutyrate 483 mg/g pellets
Trade Name	Pheburane
Pharmacologic Class	Nitrogen-binding agent
Code name	N/A
Applicant	Medunik Canada Inc.
Dosage form	Oral pellets for consumption with drink
Applicant proposed Dosing Regimen	-Patients Weighing < 20 kg: 450–600 mg/kg/day of sodium phenylbutyrate orally, equally divided into 3 to 6 doses. -Patients Weighing ≥ 20 kg: 9.9–13.0 g/m^2/day of sodium phenylbutyrate orally, equally divided into 3 to 6 doses.
Applicant Proposed Indication(s)/Population(s)	Adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies in carbamoyl phosphate synthetase, ornithine transcarbamylase, and argininosuccinic acid synthetase.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	36444000 Disorder of the urea cycle metabolism (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Same as proposed
Recommended Dosing Regimen	Same as proposed

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures: see attached document

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BE	bioequivalent
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Pheburane is a coated pellet containing 483 mg/g sodium phenylbutyrate (NaPB) that is being developed under the 505(b)(2) pathway. It has the same active ingredient as the listed drugs (LD), Buphenyl (sodium phenylbutyrate) Tablets and Powder. The LD is commercially available in the United States as Buphenyl (NDA 020572 and NDA 020573).

1.2. Conclusions on the Substantial Evidence of Effectiveness

This 505(b)(2) NDA relies on the Agency's findings of safety and effectiveness for the LD, Buphenyl (Tablets and Powder). The effectiveness of the proposed product was bridged to the LD by demonstration of similar bioavailability (bioequivalence) between sodium phenylbutyrate (Pheburane) and the LD, Buphenyl. Substantial evidence of effectiveness has previously been established for Buphenyl as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies in carbamoyl phosphate synthetase, ornithine transcarbamylase, and argininosuccinic acid synthetase.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Urea cycle disorders (UCD) are a group of genetic conditions characterized by deficiencies of the enzymes and transporters involved in the urea cycle. The severity of the defect results in the rapid accumulation of ammona. Infants with UCD appear normal at birth, but rapidly develop cerebral edema and related symptoms. Acute symptoms from hyperammonemia progress from somnolence to lethargy and coma. A significant portion of neonates with severe hyperammonemia have seizures, which may be subclinical and nonconvulsive. Hyperventilation, secondary to cerebral edema, is a common early finding in a hyperammonemic attack, which causes a respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem.

Sodium phenylbutyrate is a nitrogen scavenging product that is used to trap nitrogen into urine-excretable forms. Sodium phenylbutyrate is a pro-drug and is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine (excreted in the urine), which provides an alternate pathway for excretion of excess nitrogen.

The listed drug (LD), Buphenyl (sodium phenylbutyrate) Tablets and Powder, was approved by the FDA as a tablet in May 1996 and as a powder in April 1996 as an adjunctive therapy in the chronic management of patients with UCD involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid syntetase (AS). The Applicant submitted a 505(b)(2) application for a new product formulation for patients with UCD.. No new efficacy or safety studies were submitted as the Applicant referenced the LD for safety and efficacy. The Applicant performed two clinical bioavailability/bioequivalence (BA/BE) studies to provide a scientific bridge between the granule formulation and the LD, Buphenyl Powder. These studies were performed under both fasting and fed conditions.

In addition, the Applicant assessed safety information from two BA/BE studies in healthy volunteers, a review of the primary research articles on the use of sodium phenylbutyrate and Buphenyl, and post-marketing data obtained from the FDA Adverse Events Reporting System.. While no new adverse reactions were observed in the review of safety data from sodium phenylbutyrate pellets, post-marketing data analysis for sodium phenylbutyrate warrants safety labeling changes as reports of potential overdose with sodium phenylbutyrate were identified. It is unclear whether there was overdose in each case and whether the overdose was associated with the clinical and laboratory findings as very limited information is available for each case. However, the PI will be updated with a new section on Overdose that will include these findings with prescriber guidance for medical monitoring and interventions when needed.

In this NDA, the Applicant also suggested that sodium phenylbutyrate has been coated with a taste-masking agent, which minimizes the bitter taste of the active ingredient (b) (4) (b) (4) (b) (4) The Agency asked the Applicant to perform appropriate comparative assessments of taste between sodium phenylbutyrate 483 mg/g pellets and Buphenyl accompanied by appropriate statistical testing methodology. The Agency also requested that the Applicant include scientific data demonstrating clinical meaningfulness (b) (4) with studies showing improvements in adherence, patient intake, and safety. These studies were not submitted with the current application.

A favorable benefit-risk determination has been established previously for the LD, Buphenyl Tablets and Powder, and there are no new serious safety information that changes this favorable determination or that precludes approval of this product. Therefore, the review team recommends approval of this product.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☑	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Urea cycle disorders (UCD) are a group of genetic conditions characterized by deficiencies of the enzymes and transporters involved in the urea cycle. These include deificiencies of the enzymes carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS1), argininosuccinate lyase (ASL), and arginase (ARG1); the cofactor producer N-acetylglutamate synthase (NAGS); and the acid transporters ornithine translocase (ORNT1) and citrin (Auron and Brophy 2012). The incidence of UCDS is estimated to be 1 in 35,000 births in the United States (Summer, et al. 2013).

Severity of the UCD is influenced by the position of the defective protein in the pathway and the severity of the enzymatic deficiency. Severe deficiency or total absence of activity of CPS1, OTC, ASS1, ASL, or NAGS results in the rapid accumulation of ammonia during the first few days of life. Infants with an early-onset, severe UCD appear normal at birth, but rapidly develop life-threatening hyperammonemia that causes cerebral edema and results in neurological symptoms: vomiting, seizures, somnolence/lethargy, and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system swelling and pressure on the brain stem. Historically, the outcome of newborns with hyperammonemia was considered poor due to late diagnosis and inadequate treatment options; acute hyperammonemia from severe UCDs can progress to coma and death without treatment (Stone 2021) . In patients with late onset UCD, the initial hyperammonemic episode may be precipitated by illness or other stressor.

With earlier diagnosis and more effective treatments than dietary management alone, 5 year survival rates have improved for both early and late onset UCDs (Kido et al, 2012). Chronic disease is frequently associated with developmental/intellectual disabilities, poor linear growth, and hepatocellular injury (Batshaw et al, 2014).

2.2. Analysis of Current Treatment Options

Currently, the long-term management of UCD involves the use of a low protein diet, supplementation with essential amino acids, medications to increase waste nitrogen excretion, provision of emergency regimens during intercurrent illnesses, and orthotopic liver transplantation for selected patients (Haberle et al 2012).

Sodium phenylbutyrate is a currently approved nitrogen scavenger for chronic management of UCDs. The tablet form was approved in May 1996, and the powder form was approved in April 1996. It is dosed at 450-600 mg/kg/day in patient weighing less than 20 kg or 9.9-13 g/m^2/day in patients weighing 20 kg or more. The dose is taken in equally divided amounts with each meal or feeding.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The product has not been marketed in the United States. The product was granted Orphan Drug designation in June 2013. The LD, Buphenyl, contains the same active ingredient and was approved in 1996.

3.2. Summary of Presubmission/Submission Regulatory Activity

Presubmission activities took place under IND 121480. Since the opening protocol for this IND was permitted to proceed, a type B pre-IND meeting (April 10, 2019) was held to discuss the proposed regulatory pathway and the adequacy of the proposed 505(b)(2) NDA.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

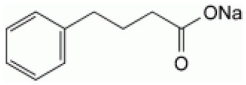
4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) determined that on-site inspections on the analytical and clinical sites used in the BE studies were not warranted for the current NDA, because Office of Regulatory Affairs (ORA) and OSIS had inspected these analytical and clinical sites under other drug applications within the surveillance interval.

4.2. Product Quality

The drug substance, Sodium Phenylbutyrate, is a white to yellowish-white powder. It has no chiral centers. It is freely soluble in water, sparingly soluble in ethanol and practically insoluble in ether. The applicant showed that the same polymorph is produced by the proposed manufacturing process.

The chemical structure, molecular formula and molecular weight of sodium phenylbutyrate are shown below.



Molecular formula: $C_{10}H_{11}NaO_2$
Molecular Weight: 186.2 g/mol

The drug substance is manufactured, tested and released as described in DMF# (b) (4) by (b) (4) The detailed CMC information including physicochemical properties, manufacturing process, characterization, specification, batch analyses of three

batches, container closure system and stability study results of the drug substance is provided in the DMF # (b) (4) from the manufacturer. A letter of authorization was provided.

A retest period for sodium phenylbutyrate of (b) (4) is acceptable (b) (4)

Pheburane is white to off-white pellets for oral administration in 250 mL plastic bottles. Each bottle contains 174 g of pellets equivalent to 84.1 g of sodium phenylbutyrate. The bottle is closed with a child-resistant twist-off cap with (b) (4) desiccant co-packaged with a calibrated dosing spoon for measurement of 0.25 g to 3.00 g in 0.25 g increment. The drug product contains the following inactive ingredients: Sugar spheres (b) (4), Hypromellose, Ethylcellulose (b) (4), Macrogol / PEG 1500 and Povidone K25.

Pheburane is manufactured (b) (4) (b) (4)

The overall control strategy for the drug product's identity, strength, purity and quality is deemed adequate based on raw material controls, manufacturing process, in-process controls and drug product specification. The release and stability specifications include the following tests: appearance by visual inspection, identity by HPLC and IR; strength by HPLC, purity via assessment of impurities by HPLC, and microbial enumeration and specified organism per USP <61> and USP <62>; (b) (4) ICP-MS and dissolution per USP <711>. A risk assessment for (b) (4) impurities indicated a low risk for the presence of (b) (4) in the drug product. In 4 lots of drug products 7 elemental impurities were found to be below ICH Q3D levels except (b) (4) Therefore, (b) (4) is controlled to NMT (b) (4) ppm per drug product specification.

The compatibility study results support that Pheburane can be sprinkled onto soft food such as apple sauce or carrot puree prior to oral administration without significant degradation in quality. The taste-masking coating starts to progressively dissolve after approximately 10 seconds thus it is recommended that Pheburane with food should be ingested immediately.

Based on the satisfactory long-term and accelerated stability study results a 36-month expiration dating period is granted when the drug product is stored at 20 to 25ºC (68 to 77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature].

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Pheburane (sodium phenylbutyrate) oral pellets, 84 g per bottle.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "**Approval**" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling is acceptable from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for "Approval".

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Sodium phenylbutyrate is one of the currently approved nitrogen-scavengers for chronic management of UCDs. It is a prodrug, metabolized by β-oxidation to phenylacetate. Phenylacetate, in turn, is conjugated with glutamine to form phenylacetylglutamine, which is excreted by the kidneys in the urine. Excretion of phenylacetylglutamine reduces ammonia accumulation in UCD by depletion of systemic glutamine, which is formed from glutamic acid and ammonia. Through this process, phenylbutyrate provides an alternate pathway for waste nitrogen excretion.

NDA 216513 was submitted under the 505(b)(2) pathway, for which the listed drug (LD) is Buphenyl.® The LD was originally approved in tablet form (April 1996) and in powder form (May 1996) as NDA 020573. Both products are administered at doses of 450-600 mg/kg/day in patients weighing 10-20 kg, or 9.9-13 g/m^2/day in patients weighing > 20 kg. Doses are divided into 3-6 per day, administered with meals/food. The maximum daily dose of sodium phenylbutyrate is 20g.

No nonclinical studies were conducted for the LD. However, administration of this novel formulation of sodium phenylbutrate at its maximal dose (20 g daily) would result in the associated dose of 1 inactive ingredient (hypromellose, or HPMC) that exceeds those in other FDA-approved products (as listed in the Inactive Ingredient Report (IIR).

The applicant did not provide evaluable information (i.e., nonclinical data) to support use of HPMC, as requested in a pre-IND meeting (April 26, 2014) with the previous sponsor, nor were qualifying nonclinical studies submitted. In response to an Information Request in the 74-day filing letter (October 2021), the Applicant submitted 5 literature citations. One of these, outlining findings from studies conducted for HPMC, was used for the current review, and found acceptable.

The maximum daily dose of HPMC in approved products, along with the amount incorporated into maximal daily Pheburane® dosing, is listed in Table 1. HPMC is an excipient that exists in food and pharmaceutical products that are generally judged safe for oral administration. It is not absorbed from the gastrointestinal tract. HPMC content in the present formulation was deemed acceptable, given the lack of toxicity associated with HPMC in a comprehensive, peer-reviewed article of nonclinical studies. Human equivalent doses (HEDs) were calculated from NOAELs in rat carcinogenicity and chronic dog studies. Safety margins based on nominal HPMC doses in adults and pediatric patients were calculated. The margins from rat and dog studies exceeded 30x and 50x, respectively, maximal daily HPMC doses in both adult and pediatric patients. The application is Approvable, from a nonclinical perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA 020573 (Buphenyl®), DMF (b) (4)

5.3. Pharmacology

Sodium phenylbutyrate is one of the currently approved nitrogen-scavengers for chronic management of UCDs. It is a prodrug, metabolized by β-oxidation to phenylacetate. Phenylacetate, in turn, is conjugated with glutamine to form phenylacetylglutamine, which is excreted by the kidneys in the urine. Excretion of phenylacetylglutamine reduces ammonia accumulation in UCD by depletion of systemic glutamine, which is formed from glutamic acid and ammonia. Through this process, phenylbutyrate provides an alternate pathway for waste nitrogen excretion.

5.4. Toxicology

5.4.1. General Toxicology: Hypromellose (HPMC) Literature referenced

Table 1. Pheburane® Hypromellose content exceeds the Maximal Daily Doses Listed in the Inactive Ingredient Report of FDA-Approved Products

	MDD in mg (as per FDA approved drugs)	MDD (mg) in Drug Product	Nominal human dose[1] (mg/kg) in drug product
Sodium Phenylbutyrate (Pheburane®)	20000	20000	333
Hypromellose 2910	1447[3]	1656	27.6

[1]Assumes 60 kg patient

[2] No nonclinical studies conducted for LD

[3] Maximum daily dose for Hypromellose (unspecified) is (b) (4)

A comprehensive review of the cellulose powders, including HPMC, was written by an unidentified author ("Anonymous") and published in the Journal of the American College of Toxicology in 1986.[i] Pertinent studies referenced within this publication are listed in Table 2

Although these studies may not have been conducted according to GLP standards, there is sufficient information to permit safety assessment of HPMC. Considering the chronic nature of Pheburane dosing for UCDs, the most cogent HPMC data are to be found in the rat carcinogenicity and 12-month dog studies. The NOAEL in the rat dietary carcinogenicity study is estimated to be 5.7 g/kg/day in males; a lower estimate is provided in female rats, since they consume less food and weigh less. The NOAEL in the longest dog study, dosed orally/directly, is 3 g/kg/day for both males and females, requiring no estimation of administered dose.

Estimates of the margins provided by the NOAELs in these nonclinical studies (for which nonclinical doses are expressed as human equivalent doses, HED), relative to the nominal human dose in adults, are detailed in Table 3. Calculation of daily Pheburane doses for pediatric patients permitted assessment of the associated HPMC intake in children; this, and calculation of the nominal pediatric dose, is outlined in Table 4. Safety Margins (HED in rat and

dog studies) relative to pediatric nominal HPMC doses at several patient weights are reproduced in Table 5.

5.5. Labeling

Highlights: Warnings and Precautions.

Table 2 HPMC Studies Listed in Journal of the American College of Toxicology 1986 Citation

Study type	Species	N /group	Doses, Route	Duration (days)	Comment	J Am Coll Toxicol Ref No,
Acute	Rat	11	Oral	-	LD50 > 4 g/kg. No toxic effects.	1
Acute	Rat	15	Oral	-	LD50 > 1 g/kg. No toxic effects	146
Acute toxicity	Mouse	138	IP	-	LD50 5 g/kg	1
Repeated dose	Rat	20	0, 2, 10, 25% in diet	30	25% associated with weight loss, mortality, diarrhea, decreased red cell count.. Endpoints of a repeated dose toxicity study. Estimate of NOAEL is 11.4 g/kg/day (in males), 6.3 g/kg/day in females[a]	1
Repeated dose	Rabbit	6	0, 2, 10, 25% in diet	30	Endpoints of repeated-dose toxicity study. Estimate of highest dose is 50 g/day = 20 g/kg/day NOAEL[b].	1
Repeated dose	Dog	1	25 or 50 g	30	Some endpoints of repeated-dose toxicity study. 50 g associated with weight loss, diarrrhea, anemia. NOAEL estimated to be 2.5 g/kg/day (in males); in females 3.125 g/kg/day.[c]	1
Subchronic	Rat	20	0.3, 10, 20% in diet	90	Combined description of 2 studies; doses between 0.3 and 10% unspecified. "Moderate growth retardation" in males @10%, 20%; and in females @ 20%.	1
Subchronic	Rat	20	0, 1, 3, 10% in diet	90	Estimate of highest dose in males is 4 g/day = NOAEL of 11.4 g/kg/day (in males).[a] ; 10.5 g/kg/day in females. All endpoints of a repeated dose toxicity study. No evidence of toxicity	186
Subchronic	Dog	4	0, 2, 6% in diet	90	Estimate of highest dose in males is 24 g/day = NOAEL of 2.4 g/kg/day (in males); in females, 2.25 g/kg/day[c] All endpoints of a repeated dose toxicity study. No evidence of toxicity.	186
Subchronic	Rat	20	0, 1, 3, 10, 30% in diet	121	50% mortality @30%, growth retardation in males at 10%. Estimate of NOAEL is 3.4 g/kg/day (in males) [a]	1
Chronic	Rat	20	0, 20, 25% in diet	365	No NOAEL. Estimated dose of 20% diet is 20 g/kg/day.	1
Chronic	Dog	2	0, 0.1, 0.3, 1, 3 g/kg/day Oral	365	No toxic effects. NOAEL 3 g/kg/day	1
Carcinogenicity	Rat	100	0, 1, 5, 20% in diet	730	50% associated with growth reduction in first years. No tumors. Estimated NOAEL = 5.7 g/kg/day (in males), 5.3 g/kg/day (in females) [a]	1

Source: Reviewer-generated.

[a] Assumptions: Mean values for body weight and food consumption in male rats are 0.35 kg and 40 g, respectively, at highest dose without adverse effects. Mean values for body weight and food consumption in female rats are 0.285 kg and 30g, respectively, at highest dose without adverse effects.

[b] Assumptions: Mean values for body weight and food consumption in rabbits are 2.5 kg and 200 g, respectively.

[c] Assumptions: Mean values for body weight and food consumption in male dogs are 10 kg and 400 g, respectively; in female dogs, 8 kg weight and 300g food consumption, respectively.

Table 3 Safety Margins for HEDs at NOAELs in Rats and Dogs, Relative to the HPMC Nominal Human Dose, for a 60 kg Patient

HPMC Nominal Dose (mg/kg) at 20,000 mg Pheburane®/day		**HPMC NOAEL $Carci_{rat}$ HED (mg/kg/day)**		**NOAEL 1 $year_{dog}$ HED (mg/kg/day)**	
		HED Males	HED Females	HED Males	HED Females
		1044	907	1661	1543
27.6	**Margin**	37.8	32.9	60.2	55.9

Source: Reviewer-generated

.

Table 4 Nominal Pediatric HPMC Dose Associated with Maximal Pheburane Doses in Pediatric Patients

Weight (kg)	**BSA (m^2)**	**Pheburane (mg)[a]**	**HPMC (mg)**	**Nominal Pediatric HPMC (mg/kg)**
48	1.4	18200	1507	31.4
36	1.2	15600	1292	35.9
22	0.85	11050	915	41.6
10	-	6000	497	49.7

Source: Reviewer-generated

[a] Assumes maximum allowed dose, as per Multi-disciplinary Review Section 2.2 (600 mg/kg/day in patients < 20 kg, or 13000 mg/m^2/day in patients > 20 kg)

Table 5 Safety Margins in Pediatric Patients Associated with HPMC HEDs at NOAELs in the Rat Carcinogenicity and 12-month Dog Studies

	HPMC HED for NOAEL $Carci_{rat}$ as calculated for pediatric weight ranges (mg/kg)		**HPMC Margins for HED $Carci_{rat}$ NOAEL for pediatric weight ranges, relative to nominal pediatric HPMC Dose**		**HPMC HED for $NOAEL_{dog}$ as calculated for pediatric weight ranges (mg/kg)**		**HPMC Margins for HED 12-$month_{dog}$ NOAEL for pediatric weight ranges, relative to nominal pediatric HPMC human dose**	
Patient weight (kg)	Males	Females	Males	Females	Males	Females	Males	Females
48	1124	976	35.8	31.1	1788	1661	56.9	52.6
36	1235	1073	34.4	29.9	1966	1826	54.8	50.9
22	1454	1263	34.9	30.4	2313	2148	55.6	51.7
10	1885	1638	37.9	33	3000	2787	60.4	56.1

Source: Reviewer-generated

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted NDA 216513 for PHEBURANE (sodium phenylbutyrate) under the 505(b)(2) pathway with BUPHENYL (BUPHENYL Powder and BUPHENYL Tablet) as the listed drug (LD). BUPHENYL (sodium phenylbutyrate) Powder was approved under NDA 020573 in April 1996. BUPHENYL (sodium phenylbutyrate) Tablet was approved under NDA 020572 in May 1996. BUPHENYL Powder and BUPHENYL Tablet currently share the same product label. BUPHENYL is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders (UCD) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid syntetase (AS). BUPHENYL must be combined with dietary protein restriction and in some cases essential amino acid supplement.

The approved recommended dosages for BUPHENYL are 450– 600 mg/kg in patients less than 20 kg and 9.9–13.0 g/m^2 in patients weighing ≥20 kg. The total daily dose is to be taken in equally divided amounts with each meal or feeding 3 to 6 times per day. The use of BUPHENYL Tablet is indicated for children weighing more than 20 kg and for adults.

The proposed product PHEBURANE is an oral pellet formulation. The Applicant proposed the same dosing regimen and same indication as BUPHENYL.

The Applicant conducted two bioequivalence (BE) studies in healthy subjects to establish a scientific bridge between PHEBURANE and BUPHENYL Powder:

- **200009:** Randomized, open-Label, two-part study to evaluate the bioequivalence between sodium phenylbutyrate 483 mg/g granules (PHEBURANE) and sodium phenylbutyrate 940 mg/g powder (BUPHENYL Powder) following a single 3 g oral dose under fasting and fed conditions in healthy adult volunteers. (Of note, the fed condition used normal-fat, normal-calorie, low-protein meals.)
- **180443:** Randomized, open-label, 3-way crossover bioequivalence and food-effect study of sodium phenylbutyrate 483 mg/g granules (PHEBURANE) versus sodium phenylbutyrate 940 mg/g powder (BUPHENYL Powder) following a single 3 g oral dose in healthy adult volunteers under fed and fasted conditions. (Of note, the fed condition used high-fat, high-calorie, low-protein meals.)

The key clinical pharmacology review findings with specific recommendations and comments are summarized in Table 2. Of note, the Applicant did not conduct relative BA studies to establish a scientific bridge between PHEBURANE and BUPHENYL Tablet. In addition to the safety information from the two BE studies in healthy volunteers, the Applicant also provided safety information based on a review of the primary research articles on the use of sodium phenylbutyrate and post-marketing data obtained from the FDA Adverse Events Reporting System. Refer to section 8.2 for safety review. The Office of Study Integrity and Surveillance (OSIS) recommended accepting the PK data without an on-site inspection (see Section 4.1).

Table 6: Summary of OCP's Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	• The effectiveness of PHEBURANE was demonstrated based on an established "bridge" via relative bioavailability data between PHEBURANE and BUPHENYL Powder. • In study 200009, BE was demonstrated between PHEBURANE and BUPHENYL Powder under fed conditions with a standardized normal calorie, normal fat, low protein meal. The 90% confidence intervals (CI) of the geometric mean ratio of C_{max} and AUC_{inf} of plasma phenylbutyrate were within the BE range of [0.80, 1.25]. • In Study 180443, under fed conditions with a high fat, high caloric meal, the 90% CI of the geometric mean ratio of AUC_{inf} for plasma phenylbutyrate was within the bioequivalent (BE) range of [0.80, 1.25]. The 90% CI of the geometric mean ratio of C_{max} was slightly higher than the BE range of [0.80, 1.25], which was not considered clinically meaningful.
General dosing instructions	• The recommended dosage measured as sodium phenylbutyrate is 450– 600 mg/kg/day in patients <20 kg, or 9.9–13.0 g/m^2/day in patients ≥20 kg. Equally divide the total daily dose into three to six doses.

	• PHEBURANE is to be taken with food. • The maximum dosage is 20 g/day because the BUPHENYL label states that safety or efficacy of doses in excess of 20 grams of sodium phenylbutyrate has not been established.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• The recommended dosage for PHEBURANE is based on individual patient's body weight and body surface area. Monitor plasma ammonia levels to determine the need for dosage adjustment within the recommended dosage range. • For patients with hepatic impairment, start at the lower end of the recommended dosing range and maintain patients on the lowest dose necessary to control plasma ammonia levels • Monitor plasma ammonia levels when starting patients with impaired renal function on PHEBURANE
Bridge between the to-be marketed and clinical trial formulations	• The to-be-marketed product/formulation was used in the clinical trials 200009 and 180443.
BE Establishment Inspection	• The Office of Study Integrity and Surveillance (OSIS) recommended accepting the PK data without an on-site inspection.

6.1.1. Recommendations:

From a Clinical Pharmacology standpoint, the NDA is acceptable to support the approval of PHEBURANE as adjunctive therapy in pediatric and adult patients with urea cycle disorders (UCD).

6.1.2. Post-Marketing Requirements and Commitments

We recommend the Applicant conduct the following PMR:

- In vitro studies to evaluate whether sodium phenylbutyrate and phenylacetate are substrates, inhibitors, or inducers of metabolizing enzymes and transporters as outlined in the FDA Guidance for Industry "In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" (January 2020). If in vitro studies suggest a potential for drug interaction, additional in vivo studies may be required.

The Applicant has agreed to conduct the PMR studies outlined above. See Section 13.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The clinical pharmacology information for PHEBURANE is primarily based on the labeling of the LD as well as the results of the BE studies conducted by the Applicant with Pheburane in healthy subjects.

Mechanism of Action
Sodium phenylbutyrate is a pro-drug and is metabolized to the active metabolite phenylacetate. Phenylacetate conjugates with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is then excreted by the kidneys hence providing an alternate vehicle for waste nitrogen excretion.

Pharmacodynamics
Sodium phenylbutyrate decreased elevated plasma ammonia and glutamine levels in patients with UCD.

Pharmacokinetics:
The PK paraemeters, including $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} , were evaluated following a single oral dose administration of PHEBURANE or BUPHENYL Powder in healthy subjects in two BE studies: 200009 and 180443.

Study 200009 is a two-part study that evaluated the PK of PHEBURANE and BUPHENYL Powder under fasting (part A) and fed (part B) conditions . The PK parameters are summarized in Table 4 and Table 5.

Study 180443 is a three-way cross over study that evaluated the PK of PHEBURANE and BUPHENYL Powder under the fed condition and additionally evaluated the effect of food on the PK of PHEBURANE. The PK parameters are summarized in Table 6.

Table 7: Pharmacokinetics of Phenylbutyrate Following A Single Oral Dose Administration of 3 Gram PHEBURANE or BUPHENYL Powder Under Fasted Condition in Healthy Subjects: Study 200009 Part A

PARAMETER	FASTED PHEBURANE (A)				FASTED BUPHENYL Powder (B)			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC_{inf} ($h^*\mu g/mL$)	37	272.1	77.3	28.4	38	287.2	70.2	24.5
AUC_{last} ($h^*\mu g/mL$)	37	270.4	77.3	28.6	38	285	70.1	24.6
C_{max} $\mu g/mL$)	37	146.3	30.4	20.8	38	166.8	25.2	15.1

Source: Reviewer's analyses using PC.XPT and PP.xpt datasets from Study 200009.
A: PHEBURANE, Sodium phenylbutyrate 1 x 6.2 g granules under fasted conditions
B: BUPHENYL Powder, Sodium phenylbutyrate 1 x 3.2 g powder under fasted conditions.

Table 8: Pharmacokinetics of Phenylbutyrate Following A Single Oral Dose Administration of 3 Gram PHEBURANE or BUPHENYL Powder Under Fed Condition in Healthy Subjects: Study 200009 Part B

PARAMETER	FED-PHEBURANE (C)				FED-BUPHENYL Powder (D)			
	N	Mean	SD	CV%	N	Mean	STD	CV%
AUC_{0-inf} ($h^*\mu g/mL$)	34	154.2	45.3	29.4	35	173.4	103.1	59.5
AUC_{0-last} ($h^*\mu g/mL$)	35	155.2	50.6	32.6	36	156.7	54.2	34.6
C_{max} $\mu g/mL$)	35	64.5	14.2	21.9	36	61.3	20.2	33

Source: Reviewer's analyses using PC.XPT and PP.xpt datasets from Study 200009
C: PHEBURANE, Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions
D: BUPHENYL Powder, Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
Note: Fed: normal-fat, normal-calorie, low-protein meals .

Table 9: Pharmacokinetics of Phenylbutyrate Following A Single Oral Dose Administration of 3 Gram PHEBURANE or BUPHENYL Powder in Healthy Subjects: Study 180443

	FED PHEBURANE(A)				FED BUPHENYL Powder (B)				FASTED-PHEBURANE (C)			
PARAMETER	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-inf} ($h^*\mu g/mL$)	23	165.9	46.7	28.2	23	157.3	68.7	43.7	23	281.7	66.7	23.7
AUC_{0-last} ($h^*\mu g/mL$)	23	152.3	43.3	28.4	23	123.7	44.1	35.7	23	271.5	63.0	23.2
C_{max} $\mu g/mL$)	23	78.5	24.5	31.1	23	68.6	29.0	42.3	23	169.0	32.6	19.3

Source: Reviewer's analyses using PC.XPT and PP.xpt datasets from Study 180443
A: PHEBURANE, Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
B: BUPHENYL Powder, Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
C: PHEBURANE Powder, Sodium phenylbutyrate 1 x 6.2 g granules under fasted conditions.
Note: Fed- High Fat, High Calorie Meals.

Food Effect

The results for the effect of food on PK of phenylbutyrate in Study 180443 are summarized in Table 7. The AUC and Cmax decreased by 40-45% and 55%, respectively, when Pheburane was given with a high-fat, high-calorie meal compared to the fasted condiction. T_{max} was found to be similar in the fed and fasted conditions. The median (range) T_{max} values for the fed and fasted conditions were 0.49 h (0.32-2.00 h) and 0.50 h (0.32-1.24 h), respectively.

Table 10: Effect of Food on the PK of Phenylbutyrate in Healthy Subjects Following A Single Oral Dose Administration of 3 Gram Pheburane: Study 180443

Parameter	**Treatment Comparisons**	**Ratio (%) Fed/Fasted**	**90% Geometric C.I.**	
			Lower (%)	**Upper (%)**
AUC_{inf}	Fed vs Fasted	0.59	0.56	0.62
AUC_{last}	Fed vs Fasted	0.55	0.52	0.58
C_{max}	Fed vs Fasted	0.45	0.41	0.50

Source: PC.XPT and PP.xpt data from Study 180443 was used by the review team to calculate least-squares means and C.I. This result is comparable with the Applicant's analyses, See Appendix 19.3.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing
The Applicant has proposed a dosage of 450 - 600 mg/kg/day in patients weighing less than 20 kg and 9.9 - 13.0 g/m^2/day in patients weight 20 kg and greater. Equally divide the total daily dose into three to six doses. PHEBURANE is to be taken with food. The proposed dosing regimens for PHEBURANE are consistent with the approved dosing regimens for the listed drug and are acceptable.

Therapeutic Individualization
The recommended dosage for PHEBURANE is based on individual patient's body weight and body surface area. Monitor plasma ammonia levels to determine the need for dosage adjustment within the recommended dosage range.

For patients with hepatic impairment, start at the lower end of the recommended dosing range and maintain patients on the lowest dose necessary to control plasma ammonia levels.
Monitor plasma ammonia levels when starting patients with impaired renal function on PHEBURANE

Outstanding Issues
There are no outstanding issues that would preclude the approval of PHEBURANE from a clinical pharmacology perspective.

In vitro and in vivo drug-drug interaction studies with phenylbutrate and metabolite phenylacetate (PAA) have not been conducted to assess whether phenylbutrate or PAA is a substrate, inhibitor, or inducer of metabolizing enzymes and transporters. The impacts of potential DDI on concomitant medications and the associated dosing adjustments are unknown. Therefore, we recommend the Applicant conduct in vitro drug-drug interaction (DDI) studies as a PMR. If in vitro studies suggest a potential for drug interaction, additional in vivo studies may be required.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of general clinical pharmacology and pharmacokinetics of PHEBURANE (sodium phenylbutyrate) is provided in Table 11. The general clinical pharmacology and pharmacokinetics of PHEBURANE were based on information from the approved product label of Buphenyl Powder and results of clinical BE studies in the current NDA.

Table 11: Summary of Clinical Pharmacology and Pharmacokinetics of PHENBURANE (Sodium Phenylbutyrate)

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	PHEBURANE is a nitrogen-binding agent.
Mechanism of action	Sodium phenylbutyrate is a pro-drug and is metabolized to phenylacetate. Phenylacetate conjugates with glutamine via acetylation to form phenylacetylglutamine which is excreted by the kidneys, providing an alternate vehicle for waste nitrogen excretion.
Active moieties	The active moiety is phenylacetate which is converted from the parent drug sodium phenylbutyrate (a sodium salt of 4-phenylbutyric acid).
	General Information
Bioanalysis	Two validated high performance liquid chromatography tandem mass spectrometry (LCMS/MS) methods were used to quantify phenylbutyrate concentrations in human plasma in PK samples collected in clinical studies. The performance of the bioanalytical methods was acceptable.
Healthy subjects vs patients	Pheburane has only been studied in healthy subjects, not in UCD patients.
Drug exposure at steady state following the therapeutic dosing regimen	The exposures of phenylbutyrate and phenylacetate at steady-state have not been characterized.
Range of effective dosage(s) or exposure	The recommended dose of Pheburane is 450– 600 mg/kg in patients <20 kg, or 9.9–13.0 g/m^2 in patients ≥20 kg in equally divided amounts 3-6 times a day.
Accumulation	The drug exposure and potential accumulation following multiple dose administration of Pheburane has not been characterized.
Time to achieve steady-state	The time to achieve steady-state has not been characterized.

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed formulation of Pheburane was evaluated in the clinical BE studies; therefore, there is no need to bridge the to-be-marketed formulation to the clinical trial formulation.
	Absorption
Bioavailability	The bioavailablity of phenylbutyrate after oral administration of PHEBURANE was similar to that after the administration of BUPEHNYL Powder. When Pheburane was administered under fed conditions (a high-fat, high-caloric meal), the Cmax and AUC of phenylbutyrate were 40-45% and 55%, respectively, of the exposuresunder fasted conditions.
T_{max}	Following a single oral dose of Pheburane (6.2 gram granules, 3 gram sodium phenylbutyate) in healthy subjects, peak plasma levels occur at 0.5 hous (median) under fed condition with a high-fat and high-calorie meal and 1.0 hour (median) under a normal-fat, normal-calorie, low-protein meal.
	Distribution
Volume of distribution	Following a single oral dose of Pheburane in healthy subjects, the apparent volume of distribution of phenylbutyrate is approximately 0.2 L/Kg.
	Elimination
Half-life	Following a single oral dose of Pheburane in healthy subjects, the mean terminal elimination half-life ($t_{1/2}$) of phenylbutyrate were approximately 0.5 hours and 1.0 hours under fasted and fed conditions, respectively.
Metabolic pathway(s)	Phenylbutyrate is metabolized to phenylacetate and subsequently to phenylacetylglutamine. The major sites for metabolism of sodium phenylbutyrate are the liver and kidney.
Primary excretion pathways (% dosage)	A majority of administered sodium phenylbutyrate (approximately 80–100%) is excreted by the kidneys within 24 hours as the conjugation product, phenylacetylglutamine. For each gram of sodium phenylbutyrate administered, it is estimated that between 0.12–0.15 grams of phenylacetylglutamine nitrogen are produced.
	Intrinsic Factors and Specific Populations

Characteristic	Drug Information
Renal impairment	No clinical trial was conducted with Pheburane to evaluate the effect of renal impairment on the PK of phenylbutyrate or its metabolite phenylacetate.
Hepatic impairment	No clinical trial was conducted with Pheburane to evaluate the effect of hepatic impairment on the PK of phenylbutyrate and its metabolite phenylacetate.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness? Do the results of the bioequivalent (BE) studies support a scientific bridging of the proposed product to the listed drug?

Yes, the effectiveness of PHEBURANE was demonstrated based on an established "bridge" via relative bioavailability data between PHEBURANE and BUPHENYL Powder. To establish a scientific bridge with Buphenyl Powder, the Applicant has compared the PK of sodium phenylbutyrate in two studies, i.e., 200009 (N=37) and 180443 (N=23), in healthy subjects following a single oral dose of 3 g sodium phenylbutyrate in the form of PHEBURANE and BUPHENYL Powder (the listed drug).

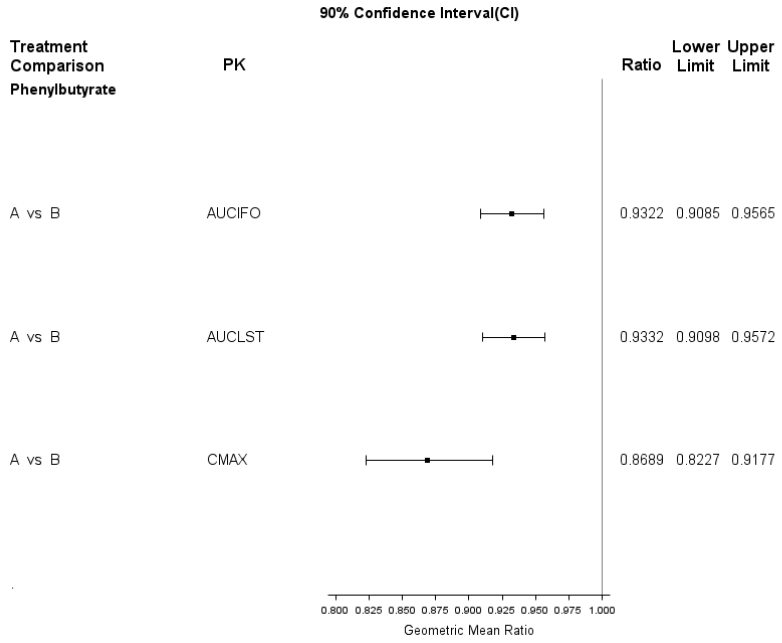
In study 200009, BE was demonstrated between PHEBURANE and BUPHENYL Powder under fed condition with a standardized normal calorie, normal fat, low protein meal. The 90% confidence intervals (CI) of the geometric mean ratio of C_{max} and AUC_{inf} of plasma phenylbutyrate were within the BE range of [0.80, 1.25].

In Study 180443, under fed condition with a high fat, high caloric meal, the 90% CI of the geometric mean ratio of AUC_{inf} for plasma phenylbutyrate was within the bioequivalent (BE) range of [0.80, 1.25]. The 90% CI of the geometric mean ratio of C_{max} was slightly higher than the BE range of [0.80, 1.25], which was not considered clinically meaningful.

Study 200009:
This was a two-part study. The first part of the study compared PK of plasma phenylbutyrate between PHEBURANE and BUPHENYL Powder under fasted condition, and the results are shown in Figure 1. The second part of the study compared PK of plasma phenylbutyrate between PHEBURANE and BUPHENYL Powder under a fed condierion, and the results are shown in Figure 2. The food condition in the second part of the study used a normal-fat, normal-calorie, low-protein breakfast. The PK results showed that

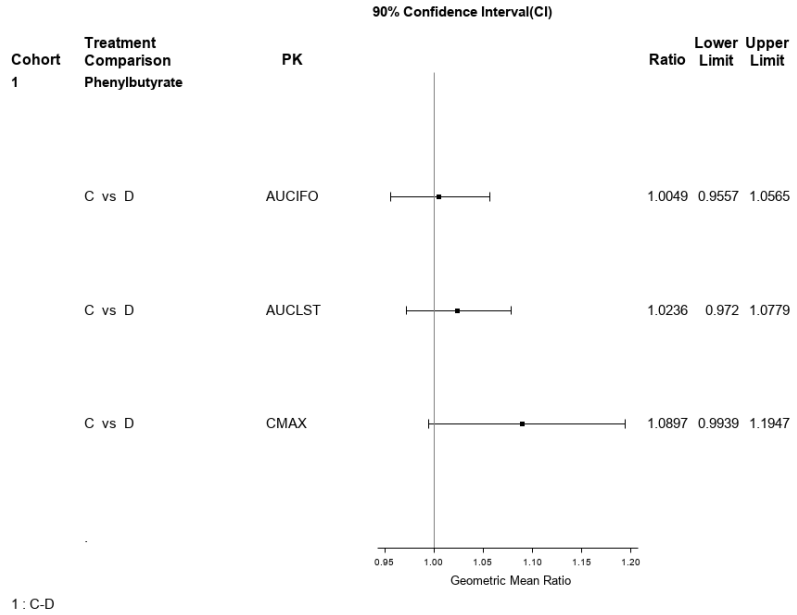
PHEBURANE in both fasted and fed conditions was bioequivalent to BUPHENYL Powder as all the PK variables including AUC_t, AUC_{inf} and C_{max} of phenylbutyrate met the BE acceptance criteria of [0.80, 1.25].

Figure 1: Comparison of Phenylbutyrate PK Between PHEBURANE and BUPHENYL Powder Under Fasted Condition in Study 200009



Treatment A (Test): PHEBURANE, Sodium phenylbutyrate 1 x 6.2 g granules under fasted condition.
Treatment B (Reference): BUPHENYL Powder, Sodium phenylbutyrate 1 x 3.2 g powder under fasted condition.
Source:. PC.XPT and PP.xpt data from Study 200009 was used by the FDA reviewer to calculate least-squares means and C.I. This result is consistent with the sponor's analyses. See Appendix 19.3.

Figure 2: Comparison of Phenylbutyrate PK Between PHEBURANE and BUPHENYL Powder Under Fed Condition in Study 200009

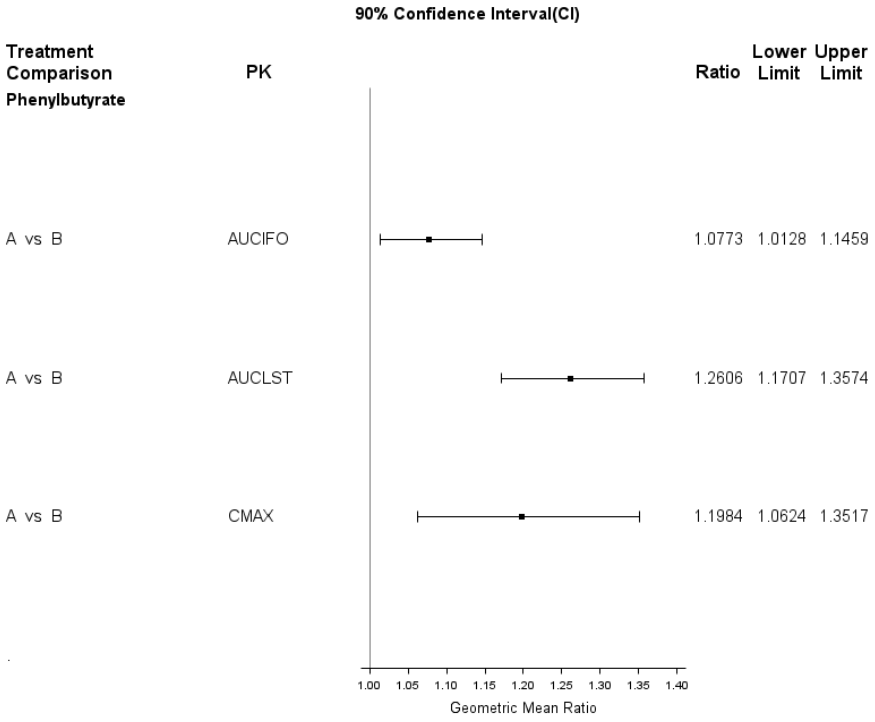


Treatment C (Test): PHEBURANE, Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment D (Reference): BUPHENYL Powder, Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
Source:. PC.XPT and PP.xpt data from Study 200009 was used by the FDA reviewer to calculate least-squares means and C.I. The result is consistent with the Applicant's analyses. See Appendix 19.3.

Study 180443:

Study 180443 was a 3-way crossover BE and food-effect study comparing PK between PHEBURANE and BUPHENYL Powder and evaluating the food effect on PK of PHEBURANE. The fed condition used high-fat, high-calorie, low-protein meals. The comparison of PK results between PHEBURANE and BUPHENYL Powder is shown in Figure 3. The point estimates of the geometric mean ratios for plasma phenylbutyrate C_{max}, AUC_{0-t} and AUC_{0-inf} were 1.20, 1.26, and 1.08, respectively, and the corresponding 90% CIs were 1.06–1.35, 1.17 – 1.36, and 1.01 – 1.15, respectively. The AUC_{0-inf} met the bioequivalent (BE) criteria of [0.80, 1.25]; however, the 90% CI for Cmax and AUC0-t was higher than the upper boundary of the BE range of 1.25.

Figure 3: Comparison of Phenylbutyrate PK Between PHEBURANE and BUPHENYL Powder Under Fed Condition in Study 180443



Treatment A (Test): PHEBURANE, Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment B (Reference): BUPHENYL Powder, Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
Source: PC.XPT and PP.xpt data from Study 180443 was used by the review reviewer to calculate least-squares means and C.I. This result is consistent with the Applicant's analyses. See Appendix 19.3.

***Reviewer's comment**: In Study 200009, BE for both $AUC_{0\text{-}inf}$ and C_{max} was demonstrated between PHEBURANE and BUPHENYL Powder under fed conditions with a standardized normal calorie, normal fat, low protein meal. In Study 180443, conducted under fed conditions with a high fat and high caloric meal, $AUC_{0\text{-}inf}$ met BE criteria but C_{max} did not meet BE criteria of [0.8, 1.25] which was not considered clinically meaningful as discussed below.*

- *From a PK perspective: In study 180443, because AUC_{0-inf} has met BE criteria, the total exposure at the recommended daily dose is expected to be similar between PHEBURANE and BUPHENYL Powder. Because the approved recommended total daily dose for the LD BUPHENYL Powder could be divided into 3 to 6 doses, fluctuations in Cmax are expected at the recommended dosing regimen. Therefore, the observed 20% difference in Cmax (with similar AUC_{0-inf}) between PHEBURANE and BUPHENYL Powder with an occasional high-fat, high-calorie meal is not considered clinically significant.*
- *From a clinical practice perspective: The management of UCD relies primarily on a diet adapted to the patient and sodium phenylbutyrate is normally administered in UCD patients with a normal-fat, normal calorie meal. Additionally, the drug should be used with dietary protein restriction and, in some cases, with dietary supplements (e.g., essential amino acids). Therefore, UCD patients are unlikely to have high-fat, high calorie food. If patients do not follow dietary protein restriction, it can lead to safety events (i.e., hyperammonemia episodes) and worsening disease. However, this risk is considered low as UCD patients are managed by experienced spcialized and experienced healthcare practitioners. Moreover, UCD patients are followed regularly by laboratory tests to monitor plasma levels of ammonia and thus adapt the medication dosage and diet to the patient's clinical and laborotary parameters.*

What are the PK characteristics of the active metabolite phenylacetate (PAA) of Pheburane?

Phenylacetate (PAA) is a metabolically active compound that conjugates with glutamine to form phenylacetylglutamine. The PK results of PAA in study 180443 showed that plasma AUC_{0-t} and C_{max} for Pheburane were slightly higher than the respective values of BUPHENYL Powder. The geometric least square mean of AUC of PHEBURANE and BUPHENYL Powder were 38.11 and 32.17 $h^*\mu g/mL$, respectively; and the geometric least square means of C_{max} of PHEBURANE and BUPHENYL Powder were 12.70 and 9.68 $\mu g/mL$, respectively. The LSM ratio (PHEBURANE/BUPHENYL Powder) and 90% geometric CI of AUC_{0-t} and C_{max} were 1.19 (1.10 to 1.29) and 1.31 (1.21 to 1.41). See more details in Appendix 19.3.3.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No clinical studies have been conducted in subjects with renal impairment or hepatic impairment to evaluate the effects of organ impairment on PK of PHEBURANE. Based on the mechanism of PHEBURANE metabolism and excretion, close monitoring ammonia levels in those patients is recommended with the following dosage adjustment and management strategy.

- Hepatic impairment. Since the conversion of phenylacetate to phenylacetylglutamine occurs in the liver, patients with hepatic impairment may have higher plasma phenylbutyrate levels due to reduced conversion capability to phenylacetylglutamine. Therefore, for patients with hepatic impairment, it is recommended to start at the lower end of the recommended dosing range and maintain the lowest dose necessary to control plasma ammonia levels.
- Renal impairment. Since a majority of administered sodium phenylbutyrate is excreted by the kidneys as phenylacetylglutamine, renal impairment may decrease the waste nitrogen excretion due to the decreased excretion of phenylacetylglutamine. It is recommended to monitor ammonia levels closely when starting patients with impaired renal function on PHEBURANE.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Compared to fasted condition, AUC of phenylbutyrate decreased by 40-45% and C_{max} of phenylbutyrate decreased by 55%, when PHEBURANE was administered with a high-fat, high-calorie meal (total 800 to 1000 calories with approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). When PHEBURANE was administered with a normal-fat, normal-calorie, low-protein meal (total 600 to 700 calories with approximately 60, 200, and 400 calories from protein, fat, and carbohydrate, respectively), AUC of phenylbutyrate decreased by 56-63% and Cmax decreased by 43-45% compared to fasted condition. See section 6.2.1. for a summary of the PK results.

There were no in vitro or clinical studies conducted evaluating the potential drug-drug interactions with PHEBURANE. Post-marketing DDI studies are recommended to assess whether PHEBURANE is substrate, inhibitor, or inducer of metabolizing enzymes and transporters. See Section 6.1.2.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 12: Clinical Trials Relevant to this NDA

Trial Identitifier	Trial Population	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	No. of Centers and Countries
Controlled Studies to Support Scientific Bridge							
20009	Healthy volunteers (18 to 58 years)	Two-period crossover BE study under fasting and fed conditions	Test drug under fasted and fed conditions (normal calorie, low protein): 6.2 g of sodium phenylbutyrate 483 mg/g pellets (total dose of 3 g) Listed drug under fasted and fed conditions (normal calorie, low protein: 3.2 g of Buphenyl (total dose of 3 g) Washout period of 7 days.	Safety: TEAEs, SAEs, physical examination, and standard lab evaluations Pharmacokinetics: BE	Single dose, oral/ 24 hours direct monitoring	40	1 center 1 country
180443	Healthy volunteers (18 years and older)	Three-period crossover BE and food effect study under fed and fasted conditions	Test drug under fed (high fat, high calorie) conditions: 6.2 g of sodium phenylbutyrate 483 mg/g pellets (total dose of 3 g) Listed drug under fed (high fat, high calorie) conditions: 3.2 g of Buphenyl (total dose of 3 g) under fed conditions Test drug under fasted: 6.2 g of sodium phenylbutyrate 483 mg/g pellets (total dose of 3 g) Washout period of 7 days	Safety: TEAEs, SAEs, physical examination, and standard lab evaluations Pharmacokinetics: BE and food effect	Single dose, oral/ 24 hours direct monitoring	24	1 center 1 country

Trial Identitifier	Trial Population	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	No. of Centers and Countries
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
LUC-1001	Healthy volunteers (18 to 55 years old)	Two-period crossover BE study of sodium phenylbutyrate 483 mg/g pellets (LUC-1) vs Ammonaps under fasting conditions	Test drug under fasted conditions: 10.21 g of coated pellets (total dose of 5 g) Listed drug under fasted conditions: 5.32 g of uncoated pellets of sodium phenylbutyrate (total dose of 5 g)	Safety: Adverse events, EKG, urine pregnancy test, vital signs, and standard lab evaluations Pharmacokinetics	Single dose, oral/ 16 hours direct monitoring	14	1 center, 1 country

Abbreviations: AE = adverse events, TEAE = treatment emergent adverse events, SAE = serious adverse events, BE = bioequivalence, EKG = electrocardiogram

7.2. Review Strategy

This application is a 505(b)(2) NDA and relies on the FDA's findings of the efficacy and safety of the LD, Buphenyl (powder and tablet); the proposed product, sodium phenylbutyrate 483 mg/g pellets, contains the same active ingredient as Buphenyl. The Applicant has submitted BA/BE studies, which were performed to assess the pharmacokinetics (PK) under fasting and fed conditions for the parent drug and the active metabolite (see Section 6.2). The Applicant provided additional safety data by searching the published literature and providing post-marketing safety data from other countries where sodium pheynylbutyrate 483 mg/g pellets are available.

The current review focuses on pharmacokinetics from the submitted BA/BE studies to establish a scientific bridge with Buphenyl powder and the available safety data for Buphenyl and sodium phenylbutyrate 483 mg/g pellets. The review also examined the comprehensive safety update from post-marketing information on the product in international markets submitted with the application, published literature, and additional submitted clinical study (LUC-1001). Safety data was pooled across all submitted studies.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 200009

Trial Design

Study 200009 was a randomized, open-label, two-part study to evaluate the BE between sodium phenylbutyrate 483 mg/g pellets and sodium phenylbutyrate 940 mg/g powder (Buphenyl) in healthy adult volunteers. Part A was a two-period, two-sequence, crossover BE study under fasting conditions. It consisted of 28 day screening period, and 34 hour confinement period. In each period, subjects were given either 6.2 g of sodium phenylbutyrate 483 mg/g pellets (total dose of 3 g) or 3.2 g of sodium phenylbutyrate 940 mg/g powder (total dose of 3 g). Part B had the same periods and sequences as Part A except it was under fed conditions (normal-fat, normal-calorie, low-protein breakfast). The investigators performed PK blood sampling and safety assessments during each period.

Study Endpoints

The primary objective of Study 200009 was to establish BE of sodium phenylbutyrate 483 mg/g pellets compared to the same dose of sodium phenylbutyrate under fasting and fed conditions using specific PK measurements as endpoints which are discussed in Section 6.2.1. The secondary objectives of the study include assessing the safety and tolerability of sodium phenylbutyrate pellets compared to sodium phenylbutyrate powder (Buphenyl).

Statistical Analysis Plan

Please see Section 6.2.1.

8.1.2. Study 180443

Trial Design

Study 180443 was a randomized, open-label, 3-way crossover study to evaluate the BE and food-effect between sodium phenylbutyrate 483 mg/g pellets and sodium phenylbutyrate 940 mg/g powder (Buphenyl) in healthy adult volunteers. The investigators performed PK blood sampling and safety assessments during each period.

Study Endpoints

The primary objective of Study 180443 was to establish BE and the effect of food of sodium phenylbutyrate 483 mg/g pellets compared to the same dose of sodium phenylbutyrate under fasting and fed conditions using specific PK measurements as endpoints which are discussed in Section 6.2.1. The secondary objectives of the study include assessing the safety and tolerability

of sodium phenylbutyrate pellets compared to sodium phenylbutyrate powder (Buphenyl).

Statistical Analysis Plan

Please see Section 6.2.1.

8.1.3. Study Information

Compliance with Good Clinical Practices

As stated in the respective CSRs, both trials were designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Financial Disclosure

The Applicant has adequatlely disclosed financial interests of clinical investigators. See financial disclosure in Appendix 19.2 for further information.

Patient Disposition

In Study 200009, four subjects did not complete the study, two for adverse events including increased body temperature and unilateral deafness. The other two discontinued for positive results on a urine drug screen.

In Study 180443, one subject did not complete the study and withdrew for personal reasons.

Protocol Deviations

In Study 200009, there were 7 protocol deviations reported. These include blood samples that were not collected (4), concomitant medications (2), and excessive water consumption (when swallowing the product). The qualified investigator determined that none would affect the results and conclusions of the study.

In Study 180443, all 24 subjects experienced protocol deviations due to the study medication not stored in an environmentally controlled room for almost 19 hours. The qualified investigator determined that this deviation would not affect the results and conclusions of the study as the temperature in the room was stable and was within allowable temperature ranges for a 24 hour period.

Table of Demographic Characteristics

The below table presents the baseline demographics for the healthy adult volunteers across the 3 trials.

Table 13: Demographic Characteristics of Healthy Volunteers in Clinical Studies

Demographic Parameters	Study 200009 (N = 40) n (%)	Study 180443 (N=34) n (%)	LUC-1001 (N=14) n (%)
Sex			
Male	19 (47.5%)	12 (50%)	6 (38.5%)
Female	21 (52.5%)	12 (50%)	8 (61.5%)
Age			
Mean years (SD)	44.9 (12.3)	44.7 (15.2)	26.2 (10.3)
Median years	46	47	*
Range (years)	23-58	18-76	*
Race			
White	40 (100%)	22 (91.7%)	14(100%)
Black or African American	0	2 (8.3%)	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Multiple	0	0	0
Ethnicity			
Hispanic or Latino	3 (7.5%)	3 (12.5%)	*
Not Hispanic or Latino	37 (92.5%)	21 (87.5%)	*

*Not included in data submitted by the Applicant.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant is relying on the Agency's past finding of safety for Buphenyl. In addition, the Applicant provided safety data from additional sources: data from four studies in healthy subjects, post-marketing data from the Applicant's reports in countries that have previously approved sodium phenylbutyrate pellets including the French Compassionate Program (ATUc) study, and published literature on sodium phenylbutyrate in UCD and non-UCD populations.

8.2.2. Review of Safety

The safety analysis included data from the Buphenyl prescribing information the clinical studies, the data from the published literature and the post-marketing safety database. The table below summarizes the safety population.

Table 14: Safety Population for Sodium Phenylbutyrate pellets and Buphenyl

Populaton	Sodium phenylbutyrate pellets (n= 311)	Buphenyl (LD) (n= 1094)

Prescribing information	n/a	206
Clinical studies in healthy volunteers	77	77
Pheburane ATUc	25	n/a
Published literature in UCD	n/a	639
Published literature in other diseases and healthy volunteers	n/a	172
Post-marketing data	209*	not specified

*Estimated based on patient-years of exposure provided by Applicant and marketing approval dates.

The review team consulted the Division of Pharmacovigilance (DPV) to evaluate postmarketing reports, including reports of overdose. DPV did not identify any new safety issues associated with use of sodium phenylbutyrate when it was dispensed and administered as indicated and intended. A discussion of overdoses is presented later in this section.Previous Findings of Safety for Buphenyl

Safety Results

The Applicant is relying on the Agency's past finding of safety for Buphenyl (tablets and powder), which can be found in the approved label for Buphenyl. The effectiveness of the proposed product was bridged to the LD by demonstration of bioequivalence of sodium phenylbutyrate to the LD based on PK parameters.The Agency agreed that this approach was acceptable.

Clinical studies

Overall Exposure

In LUC-1001, thirteen healthy adult volunteers were enrolled in a crossover BE study of 5 g coated sodium phenylbutyrate pellets vs. 5 g uncoated sodium phenylbutyrate pellets under fasting conditions. Twenty four healthy adult volunteers participated in Study 180443 in a crossover study of 3 g dose of sodium phenybutyrate pellets vs. Buphenyl under both fasting (Part A) and high-fat, high-calorie, fed conditions (Part B). In Study 20009, 40 healthy adult volunteers participated in a crossover study of 3 g sodium phenylbutyrate vs. Buphenyl under both fasting and normal-fat, normal-calorie, low-protein fed conditions. Additionally, the Applicant included safety data from the Pheburane ATUc, a pre-authorization protocol which included 25 patients with different forms of UCDs.

Issues Regarding Data Integrity and Submission Quality

There were no concerns about data quality and integrity. The datasets that the Applicant provided for the 2 BA/BE studies were accessible with analytic tools, and there was appropriate use of standard terminology. The variables were populated by expected data points. The Applicant did not submit a dataset for LUC-1001 or Pheburane ATUc.

Categorization of Adverse Events

Safety in studies 180443 and 20009 was assessed by examining AE's duration, severity and relationship to the study treatment and seriousness. Severity and relationship were rated via standardized criteria used by the contract research organization standard operating procedure. AEs were coded with Medical Dictionary for Regulatory Activities (versions 22.0 and 21.1 respectively). Safety in studies LUC-1001 were assessed by compiling AEs and coding with Medical Dictionary for Regulatory Activities (version 13.0).

There were no concerns about data quality and integrity. The datasets of the 2 BA/BE studies and LUC-1001 included by the Applicant were accessible with analytic tools, and there was appropriate use of standard terminology. The variable were populated by expected data points.

Routine Clinical Tests

Clinical laboratory tests were collected at appropriate time intervals including vital signs, laboratory tests (chemistry, hematology, urinalysis), and 12-lead electrocardiograms (ECGs). The Pheburane ATUc study did not include any specific vital sign monitoring. The safety assessment methods and time intervals are reasonable for the studied population and the indication that was investigated.

Safety Results

There were no deaths in the clinical studies submitted by the Applicant. One SAE (unilateral deafness), which also resulted in discontinuation, in Study 20009 was judged to be unrelated to the study treatment. There were no SAEs in the other clinical studies. There was one discontinuation in LUC-1001 due to vomiting judged by the investigator to be related to Buphenyl administration. The most common TEAEs in the BA/BE studies and LUC-1001 study included headache (14% of patients), nausea (12.5%), and body pain (5%), and vomiting (2.5%). . No TEAEs were reported in the Pheburane ATUc.

There were no significant laboratory or EKG findings among the clinical studies in healthy volunteers. Pheburane ATUc volunteers had significantly lower ranges of plasma ammonia and glutamine in 11 volunters after switching to the sodium phenylbutyrate pellets.

Published Literature

Overall Exposure and Adequacy of the Safety Database

The Applicant described six studies of sodium phenylbutyrate in the UCD population and eight studies in the non-UCD populations. The Applicant's literature review does not appear to be complete as more studies during the period since the LD's original approval in 1996 were available. Studies that described AEs that were not included in the safety database for the UCD population were:

- Maestri et al (1996) described UCD patients treated with 0.25-0.60 g/kg/day of sodium phenylbutyrate for 9 years. AEs reported were lethargy, irritability, and sleepiness.
- Mokhtarani, M. et al. (2013) described UCD patients treated with doses ranges from 8-13 g/day for up to 28 days. AEs reported by at least 10% of patients included diarrhea, flatulence, and headache.

There were additional studies in the non-UCD population that were not included in the review, including a study in patients with Amyotrophic Lateral Sclerosis (Cudkowicz et al., 2009), thalassemia (Hoppe et al., 1999) and acute myeloid leukemia or myelodysplasia (Maslak et al., 2006).

In spite of these omissions, the database included by the Applicant is sufficient for purposes of this safety review.

Issues Regarding Data Integrity and Submission Quality

The Applicant did not specify how these specific studies were selected for inclusion or their methods of conducting a literature review.

Routine Clinical Tests

Laboratory test findings in the summarized literature in UCD populations included acidosis, alkalosis, hypoalbuminemia, hyperphosphatemia, hypophosphatemia, and decreased plasma branched-chain amino acids (BCAA levels). Findings in non-UCD populations included hypokalemia, hyperuricemia, hyponatremia, and neutropenia.

Safety Results

The adverse events described in the literature review of Buphenyl did not vary significantly from the AEs described in the labeling of Buphenyl. These included amenorrhea, taste problems, nausea and vomiting, dyspepsia, headache, and edema.

Post-marketing Data

Overall exposure

Sodium phenylbutyrate pellets have marketing authorization as “Pheburane” in the European Union and six additional countries. The Applicant collected data from exposure to Pheburane from October 1, 2012 to December 2020, totalling 1,197.7 patient-years included in Patient Safety Update Reports (PSURs) and the latest Eurocept Signal Managment Report dated 2020.

Adequacy of the Safety Database

There is no certainty that Buphenyl or sodium phenylbutyrate caused the events reported in the safety database. Additionally, the submission of reports does not mean that the

information included has been medically confirmed or that it is an admission from the reporters that the drug caused or contributed to the event. Therefore, the information can not be used to estimate the incidence of the events reported. This uncertainty is consistent with other post-marketing sources and is adequate to support approval of the drug in conjunction with other safety data sources discussed in this section.

Categorization of Adverse Events

The events were classified as serious adverse events, deaths or other events.

Postmarketing Safety Experience

The serious adverse events reported were hyperammonemia (35%), medication use issues (35%), and vomiting (15%). Medication use issues included product use issues, underdose, medication errors, and product label confusion. Two deaths were also reported that were assessed by the Applicant to be unrelated to the product; however, the clinical data provided by the Applicant is not sufficient for the Agency to make a determination of causality. One death was deemed by the Applicant to be part of the course of the patient's unspecified congenital disease. The other death also had limited data which included the age of the patient and the the dose and frequency of administration of the drug . Information on the determined cause of death, indication, concomitant medications, duration of treatment, and comorbidities were not available. Common nonserious adverse events were off label use, medication use issues, and gastrointestinal concerns (vomiting, dyspepsia, and change in feces).

Overdose data for Sodium Phenylbutyrate

The Agency conducted a review of the National Poison Data System (NPDS), FAERS, and literature for cases of patient overdose with sodium phenylbutyrate (Food and Drug Administration 2022a, b). The available information is very limited. One case was identified in NPDS, and five additional cases were identified in FAERS:

- **Case 1 (NPDS)**: The patient was a 2-year-old male with UCD and a history of neurologic deficits who was hospitalized for fever, cyanosis and pneumonia. His ammonia level during the hospitalization was not available for review. However, during the hospitalization, he received a 12.5-fold dosing error three times over 12 hours. He developed CNS depression requiring intubation. His course also included an anion gap metabolic acidosis, hyperglycemia, hepatotoxicity, disseminated intravascular coagulopathy with thrombocytopenia. He received hemodialysis, but developed a brain bleed, herniation and died.
- **Case 2 (FAERS)**: The patient was a 5-week-old male with suspected CPS or N-acetylglutamate synthase (NAGS) deficiency who was hospitalized. His ammonia level during the hospitalization was elevated. During the hospitalization, he received 2-3 overdoses of sodium phenylbutyrate and six hours after a dose, he "spat up" and developed a decrease in his activity level that evolved into unresponsiveness. His

symptoms included emesis, progressive CNS depression requiring intubation, hepatic failure and global brain injury. Care was withdrawn, and he died.

- **Case 3 (FAERS)**: The patient was a 5-month-old male with a history of OTC deficiency who was hospitalized and had hyperammonemia. However, his ammonia level had started decreasing when he received a 5-6 fold overdose of sodium phenylbutyrate. He developed diarrhea, irritability on the same day, followed by metabolic acidosis the next day. He recovered.
- **Case 4 (FAERS)**: The patient was a 6-year-old male who was hospitalized for hyperammonemia, but his specific disease and ammonia level at the time were not available for review. He received a 7.5-fold dosing error. He developed metabolic acidosis with a compensatory respiratory alkalosis, hypokalemia, and hypophosphatemia. He recovered.
- **Case 5 (FAERS)**: The patient was a 2-year-old female with OTC deficiency who was hospitalized, but her ammonia level at the time was not available for review. She received an 8-fold dosing error, receiving 1.5 times the maximum daily recommended dose all at once. She was asymptomatic.
- **Case 6 (FAERS)**: The patient was an 18-year-old female with CPS deficiency and suspected non-compliance to Buphenyl. She was hospitalized for acute hyperammonemia, but her ammonia level was not available for review. Once the acute hyperammonemia resolved, however, she remained hospitalized for persistent tachycardia and she was restarted at her previously prescribed dose of Buphenyl (456 mg/kg/day). After 3 days of therapy, she developed encephalopathy, dysarthria, metabolic acidosis, pancreatitis, pancytopenia, and neuropathy. The healthcare team reporting the event noted in the reports that they “hypothesized that her tolerance to Buphenyl had unexpectedly decreased due to her suspected non-compliance, resulting in an “overdose.” Her dose was reduced to 125 mg/kg/day, and she “recovered after 2 months.” However, because her BSA was not available, the review team could not assess the difference between the patient’s dose and the recommended dose of sodium phenylbutyrate[SP4] and, thus, this cannot be confirmed as a case of overdose . While the patient may have had a change in her tolerance to Buphenyl, the review team can not agree that this is a true case of overdosage.

In all reported cases of potential overdose, whether the overdose was the cause for the reported symptoms and laboratory abdnormalities is unclear, and causality cannot be determined without additional information. The review team updated the overdosage section in the PI (Section 10) to reflect this information and advise that medical monitoring and procedures such as hemodialysis or veno-venous hemofiltration may be required in cases of overdose.

8.3. Statistical Issues

Refer to Section 6.3.2 for a description of the statistical analysis used in PK analysis.

8.4. Conclusions and Recommendations

In this application, the Applicant has provided sufficient PK data (based on BA/BE studies) supporting the bioequivalence of Pheburane to the LD, Buphenyl. As such, it is appropriate to rely on the Agency's findings of safety and effectiveness for Buphenyl to support approval of Pheburane. Additionally, safety data from the BA/BE studies in healthy adult volunteers, and post-marketing safety reports on use of sodium phenylbutyrate in the European Union and other countries revealed cases of potential overdose but no new serious or unexpected safety events. The reported cases of overdose lack a significant amount of detail to enable an assessment of causality and, as such, it is unclear whether there was an overdose in each case and, if so, whether any or all of the reported clinical symptoms and laboratory abnormalities were associated with the overdose or unrelated to it. A new section on Overdose is added to the PI to inform physicians about these reported cases and to provide guidance for medical interventions in the case of confirmed or suspected overdose with sodium phenylbutyrate. The new safety information does not change the favorable benefit-risk determination for the product which has been previously established for the LD, Buphenyl.

9 Advisory Committee Meeting and Other External Consultations

This application was not referred to an FDA advisory committee as no issues were identified that would benefit from outside expertise.

10 Pediatrics

The Applicant requested a waiver of the required assessments due to the Orphan Drug designation (#12-3721) for sodium phenylbutyrate 483 mg/g pellets for the treatment of urea cycle disorders per the provisions of 21 CFR 314.55(d). Buphenyl powder, the LD, is currently approved for pediatric patients across the entire pediatric age range. As such, no additional pediatric clinical studies are required.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

While the labeling for the listed drug, Buphenyl, has not been updated to meet the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) requirements, the Applicant updated labeling for this drug to meet the PLR and PLLR requirements.

See the current approved prescribing information for the final agreed upon language. A summary of significant changes is below (Table 11). Highlights and the Table of Contents were revised for consistency with the full Prescribing Information.

The changes that the review team made to the Instructions for Use and Patient Information are included in Table 12 and Table 13.

Table 15: Significant Changes Made to the Full Prescribing Information

Full Prescribing Information Section[1]	Labeling Recommendation
1 Indications and Usage	• Removed language from indication statement (b) (4) • Changed the Limitations of Use statement to reflect that Pheburane is not indicated for the treatment of acute hyperammonenia.
2 Dosage and Administration	• Re-organized information to discuss the recommended dosage, dosage adjustment/monitoring, and administration instructions in subsection 2.1, 2.2 and 2.4 respectively. • Added management of a missed dose which includes spacing doses at least 3 hours based on half-life to avoid drug accumulation and toxicity. (b) (4) • Moved statement on routine monitoring as relates to standard of care. • Moved information on monitoring plasma ammonia levels from Section 5 as it relates to effectiveness of drug. • Included specific foods (apple sauce or carrot puree) that were studied that could be used to take Pheburane. • Added considerations for dose adjustment due to potential neurotoxicity or patients with hepatic impairment (b) (4)

	[redacted] (b) (4) • Re-formatted administration instructions in subsection [redacted] (b) (4) from paragraph style to step-by-step instructions.
4 Contraindication	• [redacted] (b) (4)
5 Warnings and Precautions	• Added Subsection 5.2 titled Hypokalemia as hypokalemia was noted in post-marketing reports of sodium phenylbutyrate and phenylacetylglutamine metabolism can result in potassium loss. • [redacted] (b) (4) • Changed the Heading, [redacted] (b) (4) to Conditions Associated with Edema and changed language in order to provide instructions to clinicians who may be caring for patients with UCD and diseases that cause edema.
6 Adverse Reactions	• Re-organized information in alignment with PLR format. • Changed AR terminology and grouping to meet standardized MedDRA terminology and listed alphabetically. [redacted] (b) (4) • Moved the neurotoxicity ARs under a separate heading and placed after the listing of clinical and laboratory ARs from sodium phenylbutyrate. • [redacted] (b) (4)
7 Drug Interactions	• Re-organized information in alignment with PLR format.
8 Use In Specific Populations	• Moved the pregnancy, nursing mothers, and pediatric use information [redacted] (b) (4) of the currently approved PI to Section 8 Use in Specific Populations in order to conform to PLR and PLLR.

	• (b) (4) • • Moved neurotoxicity information (b) (4) noting that it has been observed in juvenile animals with phenylacetate exposure. • Added hepatic and renal impairment subsections.
10 Overdose	• Included new information on overdose and included statement that reported symptoms of overdose overlap with those of acute hyperammonemia. • Included information on emergency management measures for overdose.
12 Clinical Pharmacology	• Re-organized in conformance with current labeling practices and clinical pharmacology *Guidance for Industry* to provide information under subsections 12.1 Mechanism of Action, 12.2 Pharmacodynamics and 12.3 Pharmacokinetics. • (b) (4) • Added heading on Drug Interaction studies.
13 Nonclinical	• (b) (4) • •
14 Clinical Studies	• Per the PLR Format Guidance, this section is not necessary if that section was not included in the listed drug label. A "Section 14" was not included in the Buphenyl label and thus was omitted from the PHEBURANE label.
16 How Supplied	• Revised information for clarity. • (b) (4)
17 Patient Counseling Information	• Created this section to follow the Patient Counseling labeling guidance and describes all the important information needed for a healthcare

provider-patient counseling discussion.

[1] Some sections may not be included because those sections may not have major issues (or changes)

Other Prescription Drug Labeling

Table 16: Significant changes Made to Instructions for Use

IFU Section	Recommendation
Important information	• Section added
Supplies needed for measuring and taking drug	• Section added
Step 1	• (b) (4).
Step 2	• Instructions clarified for how to level oral pellets to reach prescribed dose • (b) (4)
Step 3	• Language was simplified on how to administer drug with food or drink. • Warning added not to dissolve/add pellets directly to a drink. • (b) (4)
Storing Pheburane	• Information on safe storage practices in households with children were added. • (b) (4)
Disposing of Pheburane	• Section added to provide instructions to patient on how to dispose of drug.

Table 17: Significant changes Made to Patient Information

Patient Information Section	Recommendation
(b) (4)	
What is Pheburane?	• Information to discourage use of drug in acute hyperammonemia was added.
Medical conditions to inform your physician about	• Language simplified to improve patient understanding. • Medications that may increase ammonia added to section.

How should I take Pheburane?	• Information on how to take drug was added. • Information on what to do if patient takes too much of the drug.
What are the possible side effects of Pheburane?	• Information updated to reflect adverse events, and warnings/ precautions listed in the prescribing information.
What are the ingredients in Pheburane?	• Active and inactive ingredients added.

12 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategies are required.

13 Postmarketing Requirements and Commitments

Table 15: Final, Agreed-Upon Post-Marketing Requirements

PMR	Recommended studies and key issues to be addressed	Rationale and key considerations
PMR 4293-1	In vitro studies to evaluate whether sodium phenylbutyrate and phenylacetate are substrates, inhibitors, or inducers of metabolizing enzymes and transporters as outlined in the FDA Guidance for Industry "In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" (January 2020). If in vitro studies suggest a potential for drug interaction, additional in vivo studies may be required.	The Applicant has not conducted drug-drug interaction studies with sodium phenylbutyrate or its active metabolite phenylacetate. The currently available information is not adequate to inform the drug interaction potential of sodium phenylbutyrate or phenylacetate.

14 Deputy Division Director (Clinical) Comments

I concur with the review team's assessments as described in the sections above. The Applicant has demonstrated, based on appropriately conducted BA/BE studies in healthy adults, that Pheburance is bioequivalent to the listed drug, Buphenyl (tablets and powder), on the relevant PK parameters (phenylbutyrate and its metabolite, phenylacetate). As such, it is appropriate to rely on the Agency's findings of safety and effectiveness for Buphenyl (tablets and powder) to support approval of Pheburane for the proposed indication. No new serious or unexpected clinical safety issues have emerged with post-marketing use of sodium phenylbutyrate. Reports of potential overdosage of sodium phenylbutyrate were identified, however, which may have been associated with clinical and laboratory sequelae although those are also observed in UCD patients who are hyperammonemic or otherwise sick and, as such, the relation of the clinical and laboratory findings to overdosage is unclear. The potential for overdosage is now included as a new section in the PI with instructions for medical monitoring and intervention in cases of suspected or confirmed overdose. Pheburane has orphan drug designation for the proposed indication, and, in addition, the LD, Buphenyl, is approved across the entire pediatric age range. Consequently, no additional pediatric studies are required.

15 Appendices

15.1. References

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15.2. Financial Disclosure

Covered Clinical Studies: 180443 and 20009

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 15		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in Sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Study 180443

Study 180443 is a three-way cross over design where the Applicant evaluated the relative BA/BE of PHEBURANE granule and the listed drug BUPHENYL powder under the fed condition. Additionally, PHEBURANE was given to the subjects in the fasted condition to test the effect of food on the PK of PHEBURANE. A total of 24 healthy, adult male or female, non-smoker subjects were included in this study. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme. Prior to entering the

trial, subjects had a screening visit to establish eligibility within 28 days before study drug administration. The treatment phases were separated by a washout period of 7 days.

In each period, according to the randomization scheme, subjects were administered one of the following treatments:

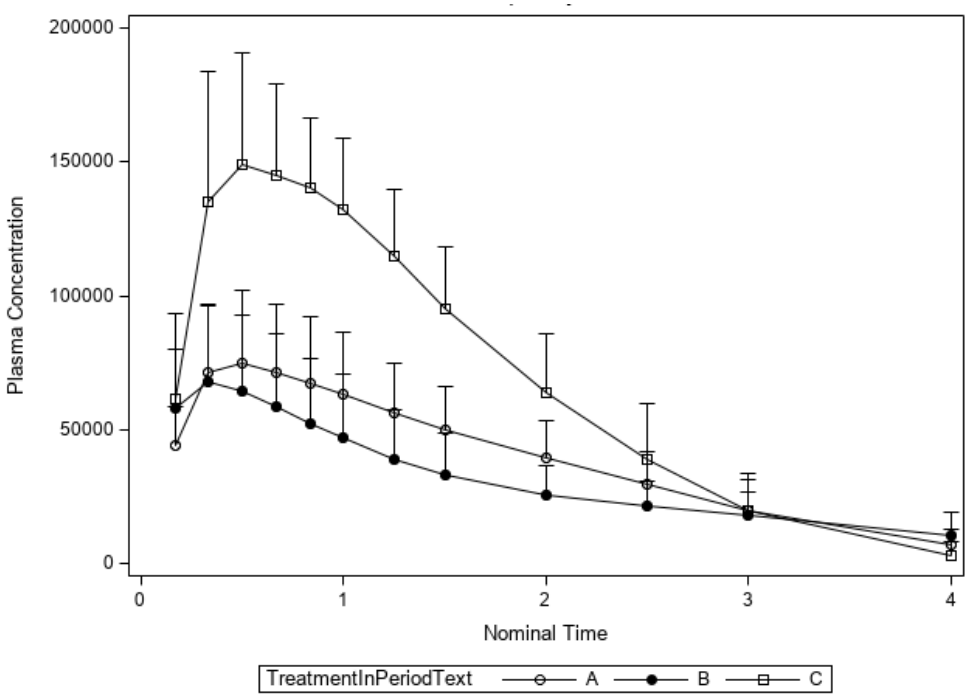
- Treatment A (Test): 1 x 6.2 g of sodium phenylbutyrate 483 mg/g granules (Pheburane, Medunik Canada Inc., Canada), for a total dose of 3 g sodium phenylbutyrate administered under fed conditions
- Treatment B (Reference): 1 x 3.2 g of sodium phenylbutyrate 940 mg/g powder (Buphenyl Powder, Horizon Pharma, Inc., USA), for a total dose of 3 g sodium phenylbutyrate administered under fed conditions
- Treatment C (Test): 1 x 6.2 g of sodium phenylbutyrate 483 mg/g granules (Pheburane, Medunik Canada Inc., Canada), for a total dose of 3 g sodium phenylbutyrate administered under fasted conditions.

Food and Fluid Intake: For Treatments A and B: After a supervised fast of at least 10 hours, subjects were served with a high-fat, high-calorie breakfast of approximately 800 to 1000 calories (approximately 50% of total caloric content of the meal derived from fat). This meal derived approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

Results:

The PK profiles of plasma phenylbutyrate are shown in Figure 4. In Study 180443, the Applicant's analysis results showed that the mean plasma AUC_{0-t} and C_{max} values of phenylbutyrate for PHEBURANE under fed condition were approximately 26% and 19% higher compared to their respective values for BUPHENYL Powder; and the upper 90% confidence intervals (CI) (135% for AUC_{0-t} and 134% for C_{max}) were above the upper limit (125%) of the BE acceptance criteria of [80, 125]. The AUC_{0-inf} of phenylbutyrate, however, met the BE criteria. The Applicant's analysis results are shown in Table 14.

Figure 4: Concentration-Time Profiles of Plasma Phenylbutyrate in Study 180443..



Plasma concentration is in ug/mL and the unit for time is hour.
Source: Generated by the reviewer team using PC.xpt dataset.

Table 18: Geometric Mean Ratios (A/B), 90% Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and p-values for Phenylbutyrate (Fed Condition) in Study 180443

Table 11.4.1-2 Ratios (A/B), 90% Geometric Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and p-values for Phenylbutyrate

		Geometric LSM			90% Geometric C.I.[2]				p-values		
Parameter (Unit)	Treatment Comparisons	Treatment A	Treatment B	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Inter Subject CV (%)	Sequence	Period	Treatment
AUC_{0-t} (h*µg/mL)	Treatment A - Treatment B	145.93	115.83	125.98	117.16	135.47	14.32	34.23	0.8698	0.2095	<0.0001
AUC_{0-inf} (h*µg/mL)	Treatment A - Treatment B	157.17	142.02	110.67	103.65	118.16	11.61	27.06	0.8270	0.9775	0.0158
C_{max} (µg/mL)	Treatment A - Treatment B	74.90	62.85	119.18	105.73	134.35	23.83	31.25	0.6543	0.3057	0.0200

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
LSM = Least squares mean.

Treatment A (Test): Medunik Canada Inc., Canada (PHEBURANE), Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment B (Reference): Horizon Pharma Inc., USA (BUPHENYL Powder), Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
Source: Table VII in Synopses individual studies (Module 2.7.2).

The effect of food was observed for the PHEBURANE when comparing its PK under fasted and fed conditions. Compared to the fasted condition, the AUCs and C_{max} decreased by 40-45% and 55% under the fed condition, respectively (Table 15).

Table 19: Geometric Mean Ratios (A/C), 90% Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and p-values for Phenylbutyrate (Food Effect) in Study 180443

		Geometric LSM			90% Geometric C.I.[2]				p-values		
Parameter (Unit)	Treatment Comparisons	Treatment A	Treatment C	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Inter Subject CV (%)	Sequence	Period	Treatment
AUC_{0-t} (h*µg/mL)	Treatment A - Treatment C	145.88	263.20	55.43	52.01	59.06	12.51	25.96	0.7189	0.6510	<0.0001
AUC_{0-inf} (h*µg/mL)	Treatment A - Treatment C	162.24	274.10	59.19	55.94	62.62	11.09	26.05	0.7212	0.8612	<0.0001
C_{max} (µg/mL)	Treatment A - Treatment C	74.96	165.41	45.32	40.92	50.20	20.26	14.45	0.4653	0.5958	<0.0001

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
LSM = Least squares mean.

Treatment A (Test): Medunik Canada Inc., Canada (PHEBURANE Powder), Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment C (Test): Medunik Canada Inc., Canada (PHEBURANE), Sodium phenylbutyrate 1 x 6.2 g granules under fasted conditions.
Source: Table VIII in Synopses individual studies (Module 2.7.2).

The PK parameters and statistical analyses of phenylacetic acid PK are Summarized in Table 16, Table 17, and Table 18.

Table 20: Descriptive Statistics Summary of Phenylacetic Acid Pharmacokinetic Parameters in Study 180443

Treatment	Analyte	Statistics	AUC_{0-t} (h*µg/mL)	AUC_{0-t} (h*µg/mL)	C_{max} (µg/mL)	Residual Area (%)	T_{max} (h)	$T_{1/2\ el}$ (h)	K_{el} (1/h)
A	PAA	N	23	7	23	7	23	7	7
		Mean	41.2	56.1	13.2	22.8	2.56	1.63	0.475
		SD	17.4	23.1	4.08	10.5	0.509	0.438	0.226
		CV%	42.2	41.3	30.8	46.1	19.9	26.8	47.6
		Min	15.1	40.8	5.24	7.78	1.49	0.707	0.353
		Median	38.9	45.6	13.1	20.0	2.49	1.77	0.392
		Max	84.8	106	21.6	36.3	4.01	1.96	0.981
		Geometric Mean	38.1	53.0	12.6	20.4	2.51	1.56	0.444
B	PAA	N	23	15	23	15	23	15	15
		Mean	35.6	55.5	10.3	33.2	2.45	2.70	0.339
		SD	16.8	20.1	3.82	21.4	0.783	1.83	0.156
		CV%	47.2	36.1	37.0	64.6	32.0	68.0	46.0
		Min	7.59	23.8	3.14	4.41	1.49	0.979	0.0896
		Median	32.1	57.0	9.01	28.1	2.49	2.03	0.342
		Max	75.9	99.5	17.0	74.0	3.99	7.73	0.708
		Geometric Mean	31.9	52.1	9.58	26.3	2.33	2.30	0.301
C	PAA	N	23	7	23	7	23	7	7
		Mean	63.6	80.4	21.6	15.4	2.53	1.23	0.636
		SD	25.0	27.6	6.52	12.6	0.499	0.537	0.197
		CV%	39.2	34.3	30.2	82.2	19.7	43.6	31.0
		Min	17.0	55.9	6.58	3.18	1.49	0.866	0.311
		Median	64.5	72.5	22.3	13.4	2.49	0.940	0.738
		Max	112	134	34.5	41.2	3.99	2.23	0.800
		Geometric Mean	58.4	77.0	20.4	11.4	2.49	1.15	0.602

N: Number of observations; SD: Standard Deviation; CV: Coefficient of variation; Min: Minimum; Max: Maximum; Treatment A (Test): Medunik Canada Inc., Canada (Pheburane), Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions; Treatment B (Reference): Horizon Pharma Inc., USA (Buphenyl), Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions; Treatment C (Test): Medunik Canada Inc., Canada (Pheburane), Sodium phenylbutyrate 1 x 6.2 g granules under fasted conditions; PAA : Phenylacetic Acid

Source: Table 4 of the Applicant's response to FDA information request received on March 3, 2022.

Table 21: Ratios (A/B), 90% Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and pvalues for Phenylacetic Acid in Study 180443

		Geometric LSM			90% Geometric C.I.[2]				p-values		
Parameter (Unit)	Treatment Comparison	Treatment A	Treatment B	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Inter-Subject CV (%)	Sequence	Period	Treatment
AUC_{0-t} (h*µg/mL)	Treatment A - Treatment B	38.41	32.17	119.39	110.48	129.01	15.30	39.83	0.1349	0.4528	0.0008
C_{max} (µg/mL)	Treatment A - Treatment B	12.70	9.68	131.17	121.83	141.24	14.58	32.41	0.2402	0.3313	<0.0001

[1] Calculated using least-squares means according ot the formula: $e^{Difference}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
LSM = Least squares mean.
Treatment A (Test): Medunik Canada Inc., Canada (Pheburane), Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment B (Reference): Horizon Pharma Inc., USA (Buphenyl), Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
Probability (p) values are derived from Type III sums of squares.
p-value for the Sequence effect is tested using the Subject(Sequence) effect as the error term.

Comparison for AUC_{0-inf} not performed since number of subjects was not sufficient for this parameter

Source: Table 5 of the applicant's response to FDA information request received on March 3, 2022.

Table 22: Geometric Mean Ratios (A/C), 90% Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and pvalues for Phenylacetic Acid in Study 180443

		Geometric LSM			90% Geometric C.I.[2]				p-values		
Parameter (Unit)	Treatment Comparison	Treatment A	Treatment C	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Inter-Subject CV (%)	Sequence	Period	Treatment
AUC_{0-t} (h*µg/mL)	Treatment A - Treatment C	38.45	58.69	65.51	61.01	70.34	14.03	35.56	0.0869	0.3108	<0.0001
C_{max} (µg/mL)	Treatment A - Treatment C	12.73	20.54	61.96	58.34	65.80	11.85	28.88	0.0819	0.0303	<0.0001

[1] Calculated using least-squares means according ot the formula: $e^{Difference}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
LSM = Least squares mean.
Treatment A (Test): Medunik Canada Inc., Canada (Pheburane), Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment C (Test): Medunik Canada Inc., Canada (Pheburane), Sodium phenylbutyrate 1 x 6.2 g granules under fasted conditions.
Probability (p) values are derived from Type III sums of squares.
p-value for the Sequence effect is tested using the Subject(Sequence) effect as the error term.

Comparison for AUC_{0-inf} not performed since number of subjects was not sufficient for this parameter

Source: Table 6 of the applicant's response to FDA information request received on March 3, 2022.

15.3.2. **Study 200009**

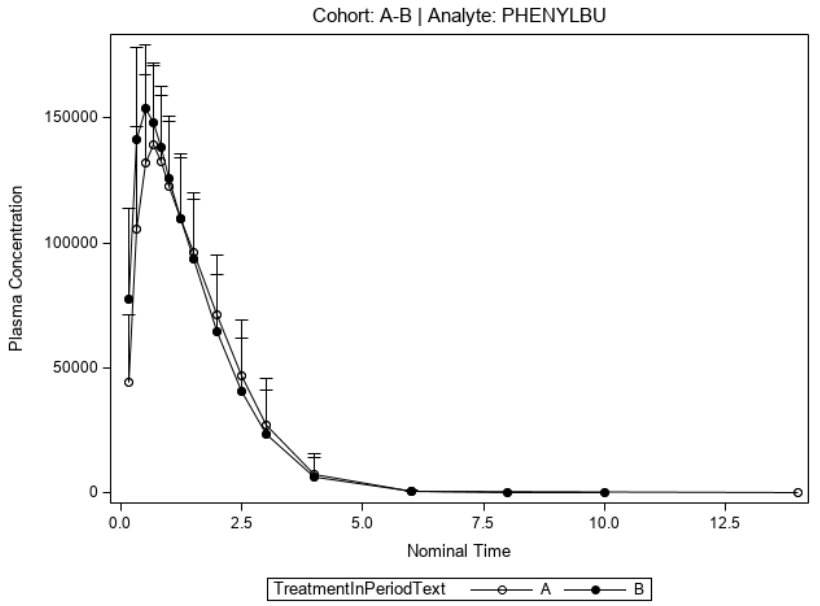
Study 200009 is a two-part study where the applicant evaluated the BA/BE of PHEBURANE and BUPHENYL Powder under fasted condition in the first part and under fed condition in the second part of the study.

Part A was a two-period, two-sequence, crossover BE study under fasted conditions and Part B was a two-period, two-sequence, crossover BE study under fed conditions where subjects were served with a normal-fat, normal-calorie, low-protein breakfast of approximately 600 to 700 calories (approximately 30% of total caloric content of the meal derived from fat). A total of 40 healthy male or female adult non-smokers (19 males and 21 females) were included in this study. The same subjects dosed in Part A were dosed in Part B. The treatment phases in each study part were separated by a washout period of 7 days. The treatment phases in each study part were separated by a washout period of 7 days. There was a washout period of 4 weeks between the last dose in Part A and the first dose in Part B.

Results:

The PK profiles for plasma phenylbutyrate are shown in Figure 5 and Figure 6. The Applicant's analysis results showed that PHEBURANE under both fasted (Part A) and fed (Part B) conditions was bioequivalent to BUPHENYL Powder and all the PK parameters including AUC_{0-t}, AUC_{0-inf} and C_{max} of phenylbutyrate met the BE acceptance criteria of [0.80, 1.25] (Table 19 and Table 20).

Figure 5: Concentration-Time Profiles of Plasma Phenylbutyrate (Fasted) in Study 200009.



Plasma concentration is in ug/mL and the unit for time is hour.
Source: Generated by review team using PC.xpt dataset.

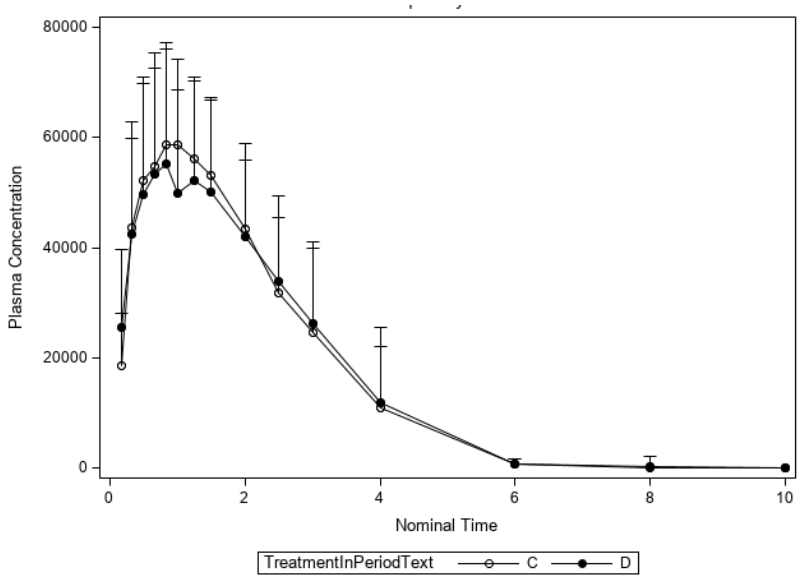
Table 23: Geometric Mean Ratios (A/B), 90% Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and p-values for Phenylbutyrate (Fasted) in Study 200009

		Geometric LSM			90% Geometric C.I.[2]				p-values		
Parameter (Unit)	Treatment Comparisons	Treatment A	Treatment B	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Inter Subject CV (%)	Sequence	Period	Treatment
AUC_{0-t} (h*ng/mL)	Treatment A - Treatment B	256337.26	274538.88	93.37	91.00	95.80	6.54	25.35	0.1358	0.7138	<0.0001
AUC_{0-inf} (h*ng/mL)	Treatment A - Treatment B	256633.33	274543.33	93.48	91.01	96.01	6.62	25.78	0.1130	0.5609	0.0002
C_{max} (ng/mL)	Treatment A - Treatment B	141900.39	162709.29	87.21	82.59	92.09	13.91	12.74	0.1837	0.2097	0.0002

[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
LSM = Least squares mean.

Treatment A (Test): Medunik Canada Inc., Canada (PHEBURANE), Sodium phenylbutyrate 1 x 6.2 g granules under fasted conditions.
Treatment B (Reference): Horizon Pharma Inc., USA (BUPHENYL Powder), Sodium phenylbutyrate 1 x 3.2 g powder under fasted conditions.
Source: Table III in Synopses individual studies (Module 2.7.2).

Figure 6: Concentration-Time Profiles of Plasma Phenylbutyrate (Fed) in Study 200009.



Plasma concentration is in ug/mL and the unit for time is hour.
Source: Generated by review team using PC.xpt dataset.

Table 24: Ratios (C/D), 90% Geometric Confidence Intervals, Intra-Subjects CV (%), Inter-Subjects CV (%) and p-values for Phenylbutyrate (Fed) in Study 200009

		Geometric LSM			90% Geometric C.I.[2]				p-values		
Parameter (Unit)	Treatment Comparisons	Treatment C	Treatment D	Ratio[1] (%)	Lower (%)	Upper (%)	Intra-Subject CV (%)	Inter Subject CV (%)	Sequence	Period	Treatment
AUC_{0-t} (h*ng/mL)	Treatment C - Treatment D	147210.18	143497.67	102.59	97.33	108.13	13.01	31.22	0.5045	0.8923	0.4172
AUC_{0-inf} (h*ng/mL)	Treatment C - Treatment D	147815.50	146255.66	101.07	96.06	106.33	11.61	28.53	0.2965	0.5126	0.7251
C_{max} (ng/mL)	Treatment C - Treatment D	62839.51	57518.38	109.25	99.52	119.93	23.27	17.04	0.1505	0.4761	0.1179

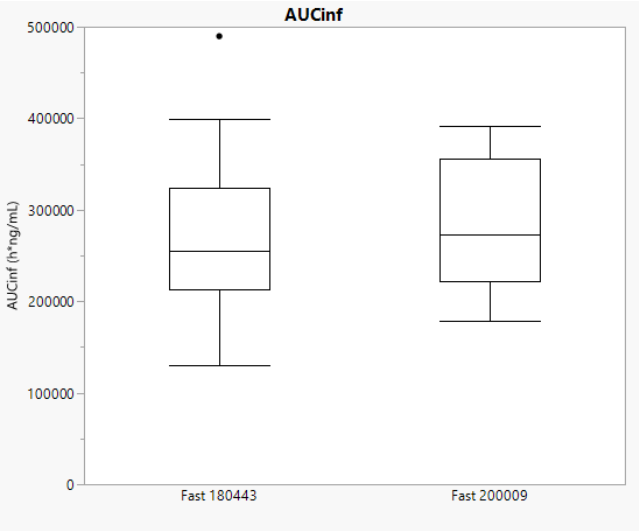
[1] Calculated using least-squares means according to the formula: $e^{Difference}$ X 100.
[2] 90% Geometric confidence interval using ln-transformed data.
LSM = Least squares mean.

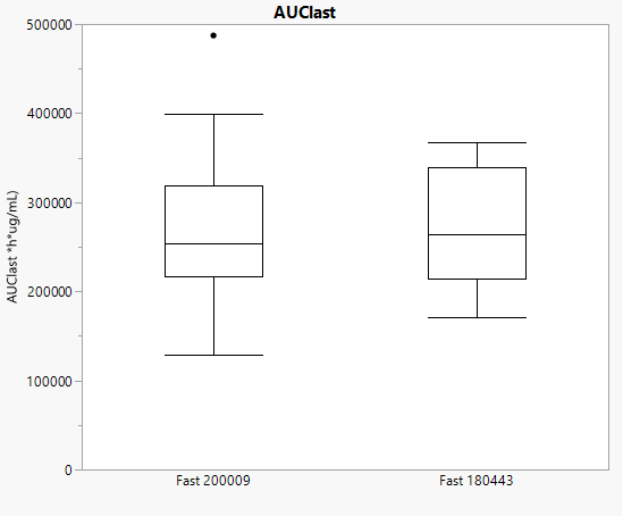
Treatment C (Test): Medunik Canada Inc., Canada (PHEBURANE), Sodium phenylbutyrate 1 x 6.2 g granules under fed conditions.
Treatment D (Reference): Horizon Pharma, Inc., USA (BUPHENYL Powder), Sodium phenylbutyrate 1 x 3.2 g powder under fed conditions.
Source: Table IV in Synopses individual studies (Module 2.7.2).

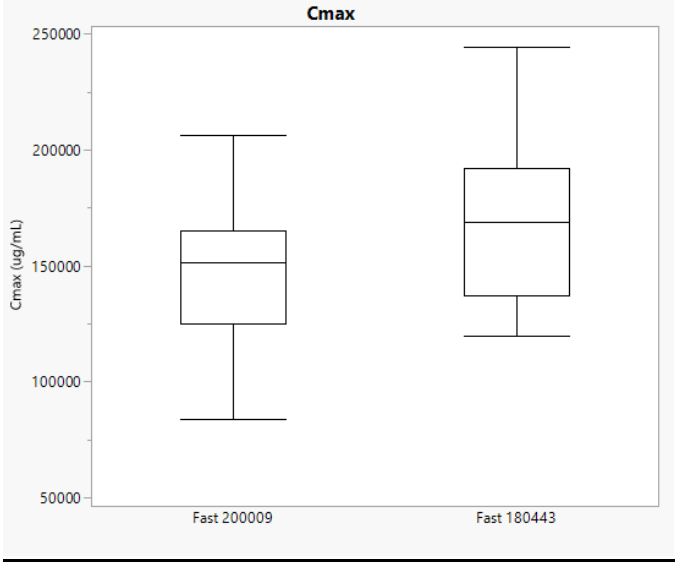
15.3.3. Cross-Study Comparisons

The pharmacokinetic parameters of sodium phenylbutyrate under fasted conditions after a single dose of Pheburane (3 g) in Study 200009 were comparable to the values observed under fasted conditions after a single dose of Pheburane (3 g) in Study 180443 (Figure 7).

Figure 7: Cross-study Comparison of the Pharmokinetic Parameters of Sodium Phenylbutyrate Granules under Fasted Conditions





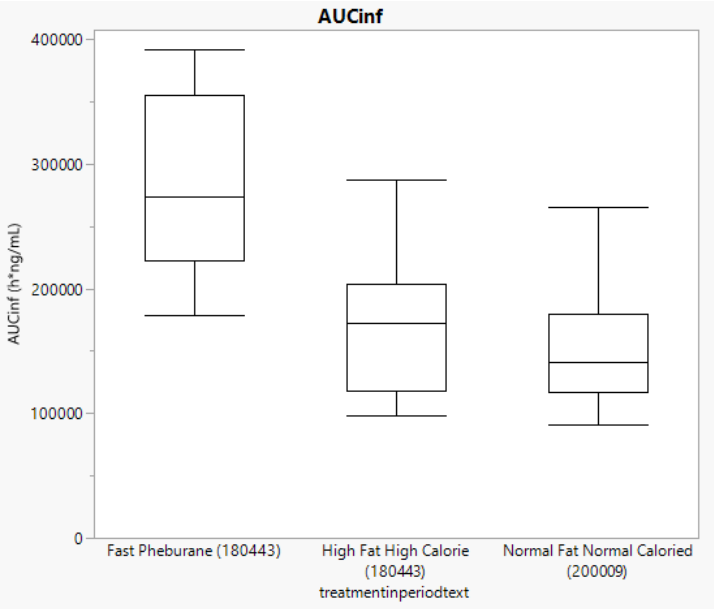


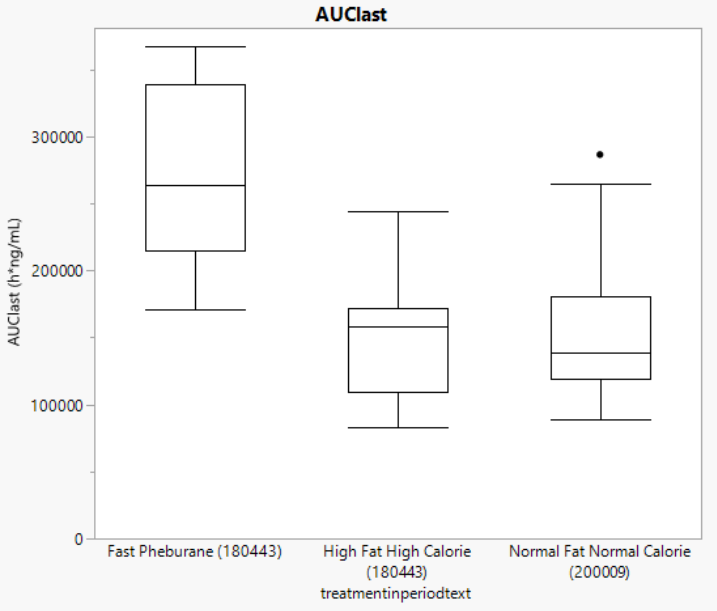
Source: Reveiwer's generated plots using PP xpt and PC xpt datasets from studies 180443 and 200009

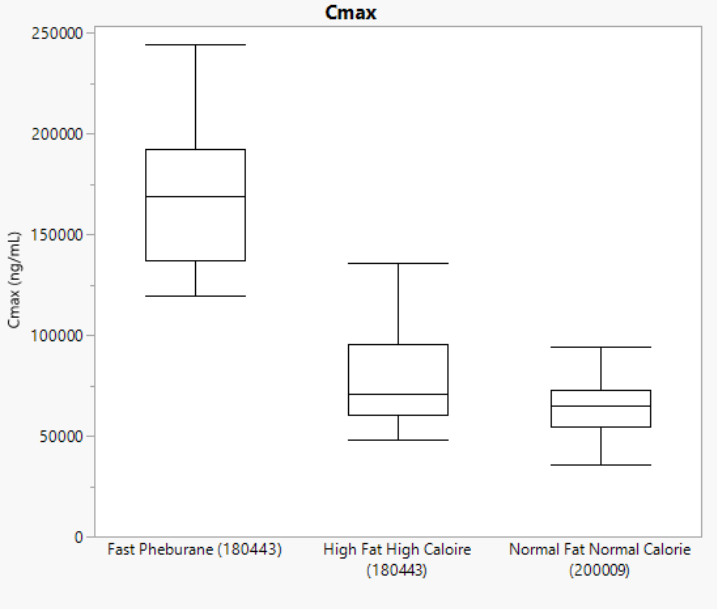
Fooed effect comparisons:

Food effect was observed in study 180443 when PHEBURANE and BUPHENYL Powder were given with a high-fat, high calorie meal. Similar food effect was also observed when PHEBURANE and BUPHENYL Powder were administered with a normal-fat, normal-calorie, low-protein breakfast in Study 200009. The rate (Cmax) and extent (AUCs) of absorption of sodium phenylbutyrate decreased (56% - 63% and 43%-45%, respectively) with a slightly delay in peak of absorption of approximately 20 to 35 minutes. Therefore, even though the food condition was different in study 180443 and study 20009, the effect of food was comparable between these two studies. Effect of different types of meal are plotted in Figure 8.

Figure 8: **Cross-study Comparison of the Effect of Food on the PK of Phenylbutyrate**







Source: Reviewer's generated plots using PP.xpt and PC.xpt from 180443 and 200009 studies.

15.3.4. Bioanalytical Methods

The Office of Clinical Pharmacology review team has assessed the the following bioanalytical methods used in clinical studies 200009 and 180443 and found the performance of the assays acceptable.

Study 200009

Concentrations of phenylbutyric acid (PBA) in human EDTA K_2 plasma were determined using a validated liquid chromatographic method with tandem mass spectrometry detection. The assay performance, validation parameters and in-study analytical report for study 200009 are summarized in Table 15.

Table 25. Bioanalytical Assay Validation Summary for Study 200009.

Bioanalytical method validation report name	Validation of a Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Phenylbutyric Acid (500 to 400000 ng/ml) in Human EDTA K_2 Plasma
Method description	(b) (4) .2841.01/02 Phenylbutyric Acid in Human EDTA K_2 Plasma over a Concentration Range of 500 to 400000 ng/mL using UPLC-MS/MS with Automated Extraction
Materials used for standard calibration curve and concentration	Two separate stock solutions were prepared from phenylbutyric acid reference material in methanol at a concentration of 80 mg/mL. One stock solution was used to prepare the calibration standards and the other was used to prepare the quality control samples. Two intermediate solutions were prepared at 20400 and 408 µg/mL in the same solvent. The intermediate solutions were then diluted at 9 different concentrations (working solutions) corresponding to 50 times (50×) the final targeted concentration in plasma for each calibrator.

	The 9 working solutions (WCS1 to WCS9) were then spiked into human EDTA K_2 plasma using a dilution scheme of 1:50 (i.e. 20 µL of WCS in 1.000 mL of plasma). The calibration standards (CS1 to CS9) final concentrations were respectively: 500.00, 1000.00, 8000.00, 20000.00, 40000.00, 80000.00, 160000.00, 320000.00 and 400000.00 ng/mL.	
Validated assay range	500.00 to 400000.00 ng/mL	
Material used for quality controls (QCs) and concentration	Two separate stock solutions were prepared from phenylbutyric acid reference material in methanol at a concentration of 80 mg/mL. One stock solution was used to prepare the calibration standards and the other was used to prepare the quality control samples. Two intermediate solutions were prepared at 20400 and 408 µg/mL in the same solvent. The intermediate solutions were then diluted at 4 different concentrations (working solutions) corresponding to 50 times (50×) the final targeted concentration in plasma for each quality control samples. The 4 working solutions (WLLQC, WQC1, WQC2 and WQC3) were then spiked into human EDTA K_2 plasma using a dilution scheme of 1:50 (i.e. 20 µL of WCS in 1.000 mL of plasma). The quality controls (LLQC, QC1, QC2 and QC3) final concentrations were respectively: 500.00, 1500.00, 200000.00 and 300000.00 ng/mL.	
Minimum required dilutions (MRDs)	Not applicable	
Source and lot of reagents	Not applicable	
Regression model and weighting	The calibration regression is linear and the weighted factor is $1/C^2$ [peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]	
Validation parameters	**Method validation summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	107
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.75 to 4.75%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 8.58%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs	-2.55 to 1.64%
	Inter-batch %CV	≤ 8.31%
	Total Error (TE)	Not applicable
Recovery	Analyte: 104.90%, 107.10% and 94.90% (CV: 1.98 to 3.10%) IS: 102.67% (CV: 1.46 and 4.15%)	
Linearity	$R^2 \geq 0.9905$	

Selectivity & matrix effect	Matrix Selectivity: 8 matrix lots were tested (including one hyperlipemic matrix and one 5% hemolyzed matrix). No significant interference observed in blank samples at the retention time of phenylbutyric acid compared to LLOQ analyte response. No significant interference observed in blank samples at the retention time of the internal standard compared to the mean IS response of accepted CS and QC samples. Matrix Effect: 8 matrix lots were tested (including one hyperlipemic matrix and one 5% hemolyzed matrix). Mean IS-Normalized matrix factor at QC1 and ULOQ levels: 1.011244 and 1.005590 CV: 3.18% and 2.26%
Interference & specificity	Potentially Interfering and Commonly Used Drugs: 13 potentially interfering and commonly used drugs were separately spiked in a QC1 sample containing phenylbutyric acid and analyzed in triplicates: acetaminophen, acetylsalicylic acid, caffeine, cotinine, dextromethorphan, dimenhydrinate, diphenhydramine, ethinyl estradiol, ibuprofen, levonorgestrel, nicotine, pseudoephedrine and salicylic acid. No effect on phenylbutyric acid quantitation. Specificity : One blank (BLKF) and one zero standard (ZS) samples were fortified with phenylacetic acid in combination with phenylacetylglutamine at their approximate expected maximal matrix concentrations. Fortified samples were processed and analyzed in triplicate to evaluate the potential interference with the phenylbutyric acid assay. No significant interference observed in BLK and ZS samples.
Hemolysis effect	One 5% hemolyzed plasma lot was tested. No significant interference observed in ZS samples at the retention time of the analyte compared to LLOQ analyte response. No significant interference observed in blank samples at the retention time of the internal standard compared to lowest IS response of accepted CS and QC samples.
Lipemic effect	One hyperlipemic plasma lot was tested. No significant interference observed in ZS samples at the retention time of the analyte compared to LLOQ analyte response. No significant interference observed in blank samples at the retention time of the internal standard compared to lowest IS response of accepted CS and QC samples.
Dilution linearity & hook effect	Dilution Integrity: A DQC sample at a concentration of 1568627.45 ng/mL was diluted in 6 replicates in human EDTA K_2 plasma with a dilution factor of 20. The mean %bias was -6.30% with a %CV of 1.87%. Hook effect: Not applicable
Bench-top/process stability	Short-Term Stability of analytes in human EDTA K_2 plasma: • 24h 45min at room temperature

	• 23h 33min at 4°C Stability of analytes in human EDTA K_2 whole blood: • 240 minutes in an ice/water bath (centrifugation at 4°C or at room temperature)
Freeze-Thaw stability	• 4 freeze and thaw cycles at -20°C • 4 freeze and thaw cycles at -80°C
Long-term storage	• Analyte in Matrix: 123 days at -20ºC • Analyte in high concentration: 169 days at -20ºC • IS in high concentration: 172 days at -20ºC • Analyte and IR in low concentration: 53 days at -20ºC
Parallelism	Not applicable
Carry over	No significant carryover observed for analyte or the IS in a blank sample preceded by a ULOQ sample
Method performance in study #200009AWVV Randomized, Open-Label, Two-Part Study to Evaluate the Bioequivalence Between Sodium Phenylbutyrate 483 mg/g Granules (Pheburane) and Sodium Phenylbutyrate 940 mg/g Powder (Buphenyl) Following a SINGLE 3 g Oral Dose under Fasting and Fed Conditions in Healthy Adult Volunteers	
Assay passing rate	A total of 16 analytical runs were analyzed in project 200009AWVV. All 16 runs were accepted.

Standard curve performance	• Cumulative bias range: -3.01 to 4.98% • Cumulative precision: ≤ 6.39% CV
QC performance	• Cumulative bias range: -2.30 to 3.96% • Cumulative precision: ≤ 10.52% CV • TE: Not applicable
Method reproducibility	Incurred sample reanalysis was performed in 7.10% (176 out of 2478 total samples) of study samples and 98.86% of samples met the pre-specified criteria
Study sample analysis/ stability	Maximum storage period of study samples: 52 days at -20°C Maximum storage period of calibration standard and QC samples: 51 days at -20°C All samples are therefore covered by a validated stability period of 123 days at -20°C.
Standard calibration curve performance during accuracy and precision runs	32 standard calibrators from LLOQ to ULOQ. (31 at CS2 level)

Source: Summary of biopharmaceutic, related bioanalytical report, analytical method validation report and bionanalytical method performance summary tables of study 200009.

Study 180443

Concentrations of phenylbutyric acid (PBA) and phenylacetic acid (PAA) in human EDTA K_2 plasma were determined using validated high performance liquid chromatographic (HPLC) methods with tandem mass spectrometry detection. The assay performance, validation parameters and in-study analytical report for study 180443 are summarized in Table 16.

Table 26. Bioanalytical Assay Validation Summary for Study 180443.

Bioanalytical method validation report name	Validation of a High Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Phenylbutyric Acid (5 to 500 µg/ml), Phenylacetic Acid (2 to 200 µg/ml) and Phenylacetylglutamine (2 to 200 µg/ml) in Human EDTA K_2 Plasma
Method description	(b) (4) 10597.03 Determination of Phenylbutyric Acid, Phenylacetic Acid and Phenylacetylglutamine in Human EDTA K_2 Plasma over Concentration Ranges of 5 to 500 µg/mL, 2 to 200 µg/mL and 2 to 200 µg/mL, respectively using High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection and using Automated Extraction
Materials used for standard calibration curve and concentration	Two separate stock solutions each of phenylbutyric acid (80 mg/mL), phenylacetic acid (32 mg/mL) and phenylacetylglutamine (32 mg/mL) were prepared in methanol and were stored at -20ºC. One stock solution was used to prepare the calibration standards and the other was used to prepare the quality control samples. Two intermediate solutions (issued from the first stock preparation) containing all three analytes were prepared at the following concentrations in methanol:

	Intermediate Solution 1	Intermediate Solution 2
Phenylbutyric acid	20 mg/mL	1 mg/mL
Phenylacetic acid	8 mg/mL	400 µg/mL
Phenylacetylglutamine	8 mg/mL	400 µg/mL

<table>
<tr><td></td><td>The first stock and intermediate solutions were then diluted at 8 different concentrations (working solutions) corresponding to 40 times (40×) the final targeted concentration in plasma for each calibrator.

The 8 working solutions (WCS1 to WCS8) were then spiked into human EDTA K_2 plasma using a dilution scheme of 1:40 (i.e. 125 µL of WCS in 5.000 mL of plasma).

The calibration standards (CS1 to CS8) final concentrations were respectively:
• 5.00, 10.00, 25.00, 50.00, 100.00, 200.00, 400.00 and 500.00 µg/mL for phenylbutyric acid
• 2.00, 4.00, 10.00, 20.00, 40.00, 80.00, 160.00 and 200.00 µg/mL for phenylacetic acid
• 2.00, 4.00, 10.00, 20.00, 40.00, 80.00, 160.01 and 200.01 µg/mL for phenylacetylglutamine.</td></tr>
<tr><td>Validated assay range</td><td>A: 5.00 to 500.00 µg/mL for Phenylbutyric acid
B: 2.00 to 200.00 µg/mL for Phenylacetic acid
C: 2.00 to 200.01 µg/mL for Phenylacetylglutamine</td></tr>
<tr><td>Material used for quality controls (QCs) and concentration</td><td>Two separate stock solutions each of phenylbutyric acid (80 mg/mL), phenylacetic acid (32 mg/mL) and phenylacetylglutamine (32 mg/mL) were prepared in methanol and were stored at -20ºC. One stock solution was used to prepare the calibration standards and the other was used to prepare the quality control samples.

Two intermediate solutions containing all three analytes were prepared at the following concentrations in methanol:
<table>
<tr><td></td><td>Intermediate Solution 1</td><td>Intermediate Solution 2</td></tr>
<tr><td>Phenylbutyric acid</td><td>20 mg/mL</td><td>1 mg/mL</td></tr>
<tr><td>Phenylacetic acid</td><td>8 mg/mL</td><td>400 µg/mL</td></tr>
<tr><td>Phenylacetylglutamine</td><td>8 mg/mL</td><td>400 µg/mL</td></tr>
</table>
The intermediate solutions (issued from the second stock preparation) were then diluted at 4 different concentrations (working solutions) corresponding to 40 times (40×) the final targeted concentration in plasma for each quality control samples.

The 5 working solutions (WLLQC, WQC1, WQC2 and WQC3) were then spiked into human EDTA K_2 plasma using a dilution scheme of 1:40 (i.e. 125 µL of WS in 5.000 mL of plasma).

The quality controls (LLQC, QC1, QC2 and QC3) final concentrations were respectively:
• 5.00, 15.00, 250,00 and 375.00 µg/mL for phenylbutyric acid
• 2.00, 6.00, 100.00 and 150.00 µg/mL for phenylacetic acid and phenylacetylglutamine</td></tr>
<tr><td>Minimum required dilutions (MRDs)</td><td>Not applicable</td></tr>
<tr><td>Source and lot of reagents</td><td>Not applicable</td></tr>
<tr><td>Regression model and weighting</td><td>The calibration regression is linear and the weighted factor is $1/C^2$ [peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]</td></tr>
<tr><td>Validation parameters</td><td>Method validation summary

A: Phenylbutyric Acid
B: Phenylacetic Acid
C: Phenylacetylglutamine</td></tr>
<tr><td>Standard calibration curve</td><td>Number of standard calibrators from LLOQ to ULOQ | 64</td></tr>
</table>

performance during accuracy and precision runs	Cumulative accuracy (%bias) from LLOQ to ULOQ	A: -2.72 to 3.01% B: -2.86 to 2.19% C: -2.18 to 1.95%
	Cumulative precision (%CV) from LLOQ to ULOQ	A: ≤ 6.62% B: ≤ 7.07% C: ≤ 9.69%

Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs**	A: -4.23 to -0.47% B: -2.56 to -1.53% C: -3.42 to -1.55%
	Inter-batch %CV	A: ≤ 10.25% B: ≤ 12.62% C: ≤ 11.39%
	Total Error (TE)	Not applicable
Linearity	A: $r^2 \geq 0.9950$ B: $r^2 \geq 0.9939$ C: $r^2 \geq 0.9926$	
Recovery	A: 87.68, 85.34, and 83.04% B: 97.27, 91.72, and 88.67% C: 91.53, 85.83, and 83.19% IS-A: 90.1% IS-B: 110.65% IS-C: 111.01%	
Selectivity & matrix effect	Matrix Selectivity: 8 matrix lots were tested (including one hyperlipemic matrix and one 5% hemolyzed matrix). No significant interference observed in ZS samples at the retention time of phenylbutyric acid, phenylacetic acid and phenylacetylglutamine compared to the corresponding LLOQ analyte response. No significant interference observed in blank samples at the retention time of the internal standards compared to the corresponding lowest IS response of accepted CS and QC samples. Matrix Effect: 8 matrix lots were tested (including one hyperlipemic matrix and one 5% hemolyzed matrix). Phenylbutyric acid: Mean IS-Normalized matrix factor at QC1 and ULOQ levels: 1.0048250 and 0.9978850 CV: 0.99% and 1.85% Phenylacetic acid: Mean IS-Normalized matrix factor at QC1 and ULOQ levels: 1.0212525 and 0.9911355 CV: 3.27% and 1.39% Phenylacetylglutamine: Mean IS-Normalized matrix factor at QC1 and ULOQ levels: 1.0192025 and 1.0157015 CV: 1.79% and 0.68%	

Interference & specificity	Potentially Interfering and Commonly Used Drugs: 13 potentially interfering and commonly used drugs were separately spiked in a QC1 sample containing phenylbutyric acid, phenylacetic acid and phenylacetylglutamine and analyzed in triplicates: acetaminophen, acetylsalicylic acid, caffeine, cotinine, dextromethorphan, dimenhydrinate, diphenhydramine, ethinyl estradiol, ibuprofen, levonorgestrel, nicotine, pseudoephedrine and salicylic acid. No effect on phenylbutyric acid, phenylacetic acid and phenylacetylglutamine quantitation. Specificity: Not applicable
Hemolysis effect	One 5% hemolyzed plasma lot was tested. No significant interference observed at the retention time of analytes compared to LLOQ analyte response. No significant interference observed at the retention time of the internal standards compared to the mean IS response of accepted CS and QC samples
Lipemic effect	One hyperlipemic plasma lot was tested. No significant interference observed at the retention time of analytes compared to LLOQ analyte response. No significant interference observed at the retention time of the internal standards compared to the mean IS response of accepted CS and QC samples
Dilution linearity & hook effect	Dilution Integrity: A DQC sample at a concentration of 1000.00 µg/mL for phenylbutyric acid and 399.99/400.00 µg/mL respectively for phenylacetic acetic/phenylacetylglutamine was diluted in 6 replicates with a dilution factor of 20. A: Bias: -0.43% and CV: 5.01% B: Bias: 2.50% and CV: 0.87% C: Bias: -0.06% and CV: 1.15% Hook effect: Not applicable

Bench-top/process stability	Short-Term Stability of analytes in human EDTA K_2 plasma: • 23h30min at room temperature • 23h34min at 4°C Stability of analytes in human EDTA K_2 whole blood: • 120 minutes in an ice/water bath
Freeze-Thaw stability	• 4 freeze and thaw cycles at -20°C • 4 freeze and thaw cycles at -80°C
Long-term storage	• Analyte in Matrix: 63 days at -20°C • Analyte in Solution -Analyte A and C (high concentration): 39 days at -20°C -Analyte (intermediate concentration): 256 days at -20°C -Analyte (low concentration): 251 days at -20°C • IS in Solution (high concentration): 172 days at -20°C
Parallelism	Not applicable
Carry over	No significant carryover observed for analytes or their respective IS in a blank sample preceded by a ULOQ sample

Method performance in study #180443AUME (Phenylbutyric Acid only) Randomized, Open-Label, 3-Way Crossover Bioequivalence and Food-Effect Study of Sodium Phenylbutyrate 483 mg/g Granules (Pheburane) Versus Sodium Phenylbutyrate 940 mg/g Powder (Buphenyl) Following a Single 3g Oral Dose in Healthy Adult Volunteers under Fed and Fasted Conditions	
Assay passing rate	A total of 13 analytical runs were analyzed in project 180443AUME. All 13 runs were accepted.
Standard curve performance	• Cumulative bias range: -2.70 to 2.67% • Cumulative precision: ≤ 4.16% CV
QC performance	• Cumulative bias range: -2.88 to 0.57 % • Cumulative precision: ≤ 4.32% CV • TE: Not applicable
Method reproducibility	Incurred sample reanalysis was performed in 9.55% (112 out of 1173 total samples) of study samples and 100.00% of samples met the pre-specified criteria
Study sample analysis/ stability	Maximum storage period of study samples: 37 days at -20°C Maximum storage period of calibration standard and QC samples: 20 days at -20°C All samples are therefore covered by a validated stability period of 63 days at -20°C

Standard calibration curve performance during accuracy and precision runs	26 standard calibrators from LLOQ to ULOQ.

Source: Summary of biopharmaceutic, related bioanalytical report, analytical method validation report and bionanalytical method performance summary tables of study 180443.

[i] Anonymous. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, and cellulose gum. J Am Coll Toxicol, 5(3): 1-59, 1986.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	216513
Supporting document/s:	001
Applicant's letter date:	August 13, 2021
CDER stamp date:	August 13, 2021
Product:	Sodium Phenylbutyrate
Indication:	Urea Cycle Disorders
Applicant:	Medunik Canada Inc
Review Division:	Division of Rare Diseases and Medical Genetics
Reviewer:	Mary Ellen McNerney, Ph.D.
Supervisor/Team Leader:	Laurie McLeod-Flynn, Ph.D.
Division Director:	Kathleen Donohue, M.D.
Project Manager:	Diego Diaz

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 216513 are owned by Medunik Canada Inc or are data for which Medunik Canada Inc has obtained a written right of reference.
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1 Executive Summary

1.1 Introduction

Urea cycle disorders (UCDs) are a group of genetic conditions characterized by deficiencies of the enzymes and transporters involved in the urea cycle. These include deficiencies of the enzymes carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinic acid synthetase (ASS), argininosuccinic acid lyase (ASL), and arginase (ARG); the cofactor producer N-acetylglutamate synthase (NAGS); and the acid transporters ornithine translocase (ORNT1) and citrin.

Severity of an UCD is influenced by the position of the defective protein in the pathway, as well as by severity of mutations contributing to enzymatic insufficiency. Severe defects or total absence of activity of CPS, OTC, ASS, ASL, or NAGS result in the rapid accumulation of ammonia during the first few days of life. Infants with an early-onset, severe UCD appear normal at birth, but rapidly develop life-threatening hyperammonemia that causes cerebral edema, with resultant neurological symptoms: vomiting, seizures, somnolence/lethargy, and coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system edema and pressure on the brain stem. A significant proportion of neonates with severe hyperammonemia have seizures, which may be subclinical/ nonconvulsive. Hyperventilation, secondary to cerebral edema, is a common early finding in a hyperammonemic attack, which causes respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem.

Currently, the long-term management of UCD involves dietary measures (including low protein intake and supplementation with essential amino acids); medications to increase waste nitrogen excretion; provision of emergency regimens during intercurrent illnesses; and orthotopic liver transplantation for selected patients.

Sodium phenylbutyrate is one of the currently approved nitrogen-scavengers for chronic management of UCDs. It is a prodrug, metabolized by β-oxidation to phenylacetate. Phenylacetate, in turn, is conjugated with glutamine to form phenylacetylglutamine, which is excreted by the kidneys in the urine. Excretion of phenylacetylglutamine reduces ammonia accumulation in UCD by depletion of systemic glutamine, which is formed from glutamic acid and ammonia. Through this process, phenylbutyrate provides an alternate pathway for waste nitrogen excretion.

NDA 216513 was submitted under the 505(b)(2) pathway, for which the listed drug (LD) is Buphenyl.® The LD was originally approved in tablet form (April 1996, NDA 020572) and in powder form (May 1996, NDA 020573. Both products are administered at doses of 450-600 mg/kg/day in patients weighing 10-20 kg, or 9.9-13 g/m^2/day in patients weighing > 20 kg. Doses are divided into 3-6 per day, administered with meals/food. The maximum daily dose of sodium phenylbutyrate is 20g.

No nonclinical studies were conducted for the LD. However, administration of this novel formulation of sodium phenylbutrate at its maximal dose (20 g daily) would result in an associated doses of 1 inactive ingredient that exceeds quantities in other FDA-approved products (as listed in the Inactive Ingredient Report (IIR)): hypromellose (aka hydroxypropylmethylcellulose (HPMC)). Pertinent information is reviewed in **Table 1**.

The applicant did not provide evaluable information for HPMC, as requested in a pre-IND meeting (April 26, 2014) with a previous sponsor; nor were qualifying nonclinical studies submitted. In response to an Information Request in the 74-day filing letter (October 2021), the Applicant submitted 5 literature citations. One of these, outlining findings from studies conducted for HPMC, was used for the current review.

1.2 Brief Discussion of Nonclinical Findings for Excipient Qualification

HPMC is an excipient in food and pharmaceutical products that are generally judged safe for oral administration. It is not absorbed from the gastrointestinal tract. In large doses (g/kg/day), it may interfere with absorption of food and nutrients. The dose proposed for HPMC use in Pheburane® does not approach these levels.

An overview of HPMC nonclinical data summaries is included in Table 2. The results of HED calculations associated with the NOAELs in rat carcinogenicity and chronic dog studies (for the adult Pheburane® maximum daily dose) are represented in Table 3. Calculation of nominal HPMC pediatric doses associated with Pheburane® pediatric dosing is included in Table 4, and safety margins associated with these nominal pediatric doses, relative to the rat and dog HEDs of NOAELs, are represented in Table 5. Pediatric margins relative to the HED from the rat carcinogenicity study are ≥ 30x, while margins relative to the HED from the chronic dog study are ≥ 50x.

Table 1 Pheburane® HPMC Content Exceeds Maximal Daily Doses Listed in the Inactive Ingredient Report of FDA-Approved Products, with Results of Literature Reports Used for Qualification

	MDD in mg (as per FDA approved drugs)	MDD (mg) in Drug Product	Nominal human dose[1] (mg/kg) in drug product	Rat NOAEL (mg/kg)[2, 3]		HED_{rat} (mg/kg)		Dog NOAEL (mg/kg)[4]		HED_{dog}		$Margin_{rat}$		$Margin_{dog}$	
Sodium Phenylbutyrate	20000	20000	333												
Hypromellose 2910	1447	1656	27.6	M[5]	F[6]	M	F	M	F	M	F	M	F	M	F
				5700	5300	1044	907	3000	3000	1661	1543	37.8	32.9	60.2	55.9

[1] Assumes 60 kg patient
[2] No nonclinical studies conducted for LD.
[3] NOAELs estimated from a dietary carcinogenicity study, Anonymous et al., 1986
[4] Data for dog study are from a 12-month study, Anonymous et al, 1986
[5] Male
[6] Female

Source: Reviewer-generated

1.3 Recommendations

The Applicant relied on FDA findings of safety for sodium phenylbutyrate as determined for the LD.

Excipient doses are acceptable. Literature was used to qualify HPMC doses contained in Pheburane®.

1.3.1 Approvability

This product is approvable from the nonclinical perspective.

1.3.2 Additional Non-Clinical Recommendations

None.

1.3.3 Labeling.

(b) (4)

[redacted]

[1] Lacey DJ. Cortical dendritic spine loss in rat pups whose mothers w whose mothers were prenatally injected with phenylacetate ("maternal PKU" model). Dev Brain Res, 27:283-285, 1986.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number (Optional). 1716-12-7.

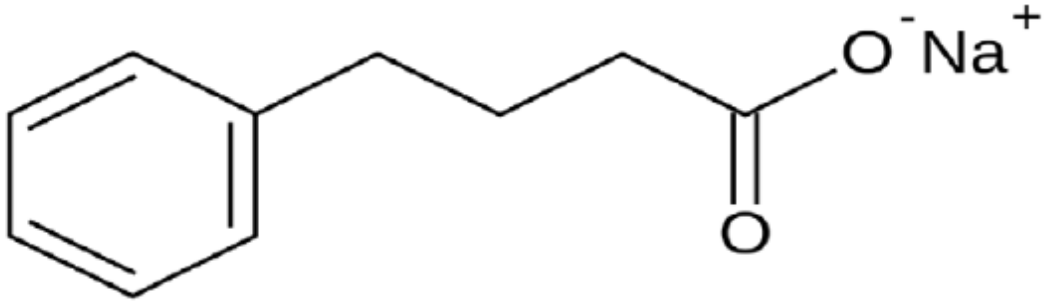
Generic Name. Sodium Phenylbutyrate

Code Name ACER-001.

Chemical Name. 4-Phenylbutyrate Sodium

Molecular Formula/Molecular Weight. $C_{10}H_{11}NaO_2$

Structure or Biochemical Description



Pharmacologic Class. Nitrogen-binding agent.

[2] Wen GY, Wisniewski HM, Shek JW et al. Neuropathology of phenylacetate poisoning in rats: an experimental model of phenylketonuria. Ann Neurol 7: 557-566, 1980.

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 121480, NDA 020573 (Buphenyl®), DMF (b) (4)

2.3 Drug Formulation

Not applicable.

2.4 Comments on Novel Excipients

HPMC: Considered qualified, as per literature

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical Population: UCD Patients.
Maximum Recommended Pheburane® dose: 600 mg/kg/day in patients < 20 kg, or 13000 mg/m^2/day in patients > 20 kg

2.7 Regulatory Background

U.S. Regulatory Actions and Marketing History
The initial IND application for sodium phenylbutyrate 483 mg/g pellets was submitted in August 2019 for the chronic management of patients with UCD. The product has not been marketed in the United States. The product was granted Orphan Drug designation in June 2013. The LD, Buphenyl, contains the same active ingredient that was approved in 1996.

Summary of Pre-submission/Submission Regulatory Activity
Pre-submission activities took under IND 121480. The opening protocol for this IND was permitted to proceed. A type B pre-NDA meeting (April 10, 2019) was held to discuss the proposed regulatory pathway and the adequacy of the proposed 505(b)(2) NDA.

3 Studies Submitted

None

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

None.

3.3 HPMC: Literature Referenced.

A comprehensive review of the cellulose powders, including HPMC, was written by an unidentified author (“Anonymous”) and published in the Journal of the American College of Toxicology in 1986.[i] Pertinent studies referenced within this publication are listed in Table 2.

Although these studies may not have been conducted according to GLP standards, there is sufficient information to permit safety assessment of HPMC. Considering the chronic nature of Pheburane dosing for UCDs, the most cogent HPMC data are to be found in the rat carcinogenicity and 12-month dog studies. The NOAEL in the rat dietary carcinogenicity study is estimated to be 5.7 g/kg/day in males; a lower estimate is provided in female rats, since they consume less food and weigh less. The NOAEL in the longest dog study, dosed orally/directly, is 3 g/kg/day for both males and females, requiring no estimation of administered dose.

Estimates of the margins provided by the NOAELs in these studies (expressed as human equivalent doses, HED), relative to the nominal human dose in adults, are detailed in Table 3. Calculation of daily Pheburane doses for pediatric patients permitted assessment of the associated HPMC intake in children; this, and calculation of the nominal pediatric dose, is outlined in Table 4. Safety Margins (HED in rat and dog studies) relative to pediatric nominal HPMC doses at several patient weights are reproduced in Table 5.

Table 2 HPMC Studies Listed in Journal of the American College of Toxicology 1986 Citation

Study type	Species	N /group	Doses, Route	Duration (days)	Comment	J Am Coll Toxicol Ref No,
Acute	Rat	11	Oral	-	LD50 > 4 g/kg. No toxic effects.	1
Acute	Rat	15	Oral	-	LD50 > 1 g/kg. No toxic effects	146
Acute toxicity	Mouse	138	IP	-	LD50 5 g/kg	1
Repeated dose	Rat	20	0, 2, 10, 25% in diet	30	25% associated with weight loss, mortality, diarrhea, decreased red cell count.. Endpoints of a repeated dose toxicity study. Estimate of NOAEL is 11.4 g/kg/day (in males), 6.3 g/kg/day in females[a]	1
Repeated dose	Rabbit	6	0, 2, 10, 25% in diet	30	Endpoints of repeated-dose toxicity study. Estimate of highest dose is 50 g/day = 20 g/kg/day NOAEL[b].	1
Repeated dose	Dog	1	25 or 50 g	30	Some endpoints of repeated-dose toxicity study. 50 g associated with weight loss, diarrrhea, anemia. NOAEL estimated to be 2.5 g/kg/day (in males); in females 3.125 g/kg/day.[c]	1
Subchronic	Rat	20	0.3, 10, 20% in diet	90	Combined description of 2 studies; doses between 0.3 and 10% unspecified. "Moderate growth retardation" in males @10%, 20%; and in females @ 20%.	1
Subchronic	Rat	20	0, 1, 3, 10% in diet	90	Estimate of highest dose in males is 4 g/day = NOAEL of 11.4 g/kg/day (in males).[a] ; 10.5 g/kg/day in females. All endpoints of a repeated dose toxicity study. No evidence of toxicity	186
Subchronic	Dog	4	0, 2, 6% in diet	90	Estimate of highest dose in males is 24 g/day = NOAEL of 2.4 g/kg/day (in males); in females, 2.25 g/kg/day[c] All endpoints of a repeated dose toxicity study. No evidence of toxicity.	186
Subchronic	Rat	20	0, 1, 3, 10, 30% in diet	121	50% mortality @30%, growth retardation in males at 10%. Estimate of NOAEL is 3.4 g/kg/day (in males) [a]	1
Chronic	Rat	20	0, 20, 25% in diet	365	No NOAEL. Estimated dose of 20% diet is 20 g/kg/day.	1
Chronic	Dog	2	0, 0.1, 0.3, 1, 3 g/kg/day Oral	365	No toxic effects. NOAEL 3 g/kg/day	1
Carcinogenicity	Rat	100	0, 1, 5, 20% in diet	730	50% associated with growth reduction in first years. No tumors. Estimated NOAEL = 5.7 g/kg/day (in males), 5.3 g/kg/day (in females) [a]	1

Source: Reviewer-generated.
[a] Assumptions: Mean values for body weight and food consumption in male rats are 0.35 kg and 40 g, respectively, at highest dose without adverse effects. Mean values for body weight and food consumption in female rats are 0.285 kg and 30g, respectively, at highest dose without adverse effects.
[b] Assumptions: Mean values for body weight and food consumption in rabbits are 2.5 kg and 200 g, respectively.
[c] Assumptions: Mean values for body weight and food consumption in male dogs are 10 kg and 400 g, respectively; in female dogs, 8 kg weight and 300g food consumption, respectively.

Table 3 Safety Margins for HEDs at NOAELs in Rats and Dogs, Relative to the HPMC Nominal Human Dose, for a 60 kg Patient

HPMC Nominal Dose (mg/kg) at 20,000 mg Pheburane®/day		**HPMC NOAEL $Carci_{rat}$ HED (mg/kg/day)**		**NOAEL 1 $year_{dog}$ HED (mg/kg/day)**	
		HED Males	HED Females	HED Males	HED Females
		1044	907	1661	1543
27.6	**Margin**	37.8	32.9	60.2	55.9

Source: Reviewer-generated
.

Table 4 Nominal Pediatric HPMC Dose Associated with Maximal Pheburane Doses in Pediatric Patients

Weight	**BSA**	**Pheburane (mg)[a]**	**HPMC (mg)**	**Nominal Pediatric HPMC dose (mg/kg/day)**
48	1.4	18200	1507	31.4
36	1.2	15600	1292	35.9
22	0.85	11050	915	41.6
10	-	6000	497	49.7

Source: Reviewer-generated
[a] Assumes maximum allowed dose, as per Multi-disciplinary Review Section 2.2 (600 mg/kg/day in patients < 20 kg, or 13000 mg/m^2/day in patients > 20 kg)

Table 5 Safety Margins in Pediatric Patients Associated with HPMC HEDs at NOAELs in the Rat Carcinogenicity and 12-month Dog Studies

	HPMC HED for NOAEL $Carci_{rat}$ as calculated for pediatric weight ranges (mg/kg/day)		**HPMC Margins for HED $Carci_{rat}$ NOAEL for pediatric weight ranges, relative to nominal pediatric HPMC Dose**		**HPMC HED for $NOAEL_{dog}$ as calculated for pediatric weight ranges (mg/kg/day)**		**HPMC Margins for HED 12-$month_{dog}$ NOAEL for pediatric weight ranges, relative to nominal pediatric HPMC human dose**	
Patient weight (kg)	Males	Females	Males	Females	Males	Females	Males	Females
48	1124	976	35.8	31.1	1788	1661	56.9	52.6
36	1235	1073	34.4	29.9	1966	1826	54.8	50.9
22	1454	1263	34.9	30.4	2313	2148	55.6	51.7
10	1885	1638	37.9	33	3000	2787	60.4	56.1

Source: Reviewer-generated

[i] Anonymous. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, and cellulose gum. J Am Coll Toxicol, 5(3): 1-59, 1986.

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