AUSTRALIAN PRODUCT INFORMATION –

PHEBURANE™ sodium phenylbutyrate granules

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1. NAME OF THE MEDICINE

Sodium phenylbutyrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pheburane® granules are sugar-coated spheres containing sodium phenylbutyrate

Each gram of granules contains 483 mg of sodium phenylbutyrate.

Excipient(s) with known effect:

Each gram of sodium phenylbutyrate contains 124 mg (5.4 mmol) of sodium and 768 mg of sucrose. For the full list of excipients, see section 6.1 LIST OF INGREDIENTS

3. PHARMACEUTICAL FORM

Granules.
White to off-white granules.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pheburane (sodium phenylbutyrate) is indicated for the management of hyperammonaemia associated with urea cycle disorders. Pheburane® should be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, and protein-free calorie supplements)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosing Considerations

Pheburane treatment should be initiated and supervised by a health professional experienced in the treatment of urea cycle disorders, as part of a multidisciplinary team.

The daily dose should be individually adjusted according to the patient's protein tolerance and the daily dietary protein intake needed to promote growth and development.

Recommended Dose and Dosage Adjustment

The usual total daily dose of sodium phenylbutyrate is:

- up to 600 mg/kg/day in neonates, infants and children weighing less than 20 kg;
- up to 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults. The safety and efficacy of doses in excess of 20 g/day have not been established.

The recommended dose is expressed in terms of milligrams (mg) or grams (g) of sodium phenylbutyrate, rather than the weight of the granules.

A calibrated dosing spoon is provided which dispenses PHEBURANE granules equivalent to amounts up to 3 g of sodium phenylbutyrate in graduations of 250 mg.

Use ONLY the dosing spoon provided with the medicine to measure out the dose. DO NOT use any other measuring device to measure out the dose.

The total daily dose of Pheburane should be divided into equal amounts and given with each meal or feeding (e.g. 4-6 times per day in small children). The granules can be directly swallowed with a drink (water, fruit juices, protein-free infant formulas) or sprinkled on to a spoonful of solid food (mashed potatoes or apple sauce); in this case, it is important that the Pheburane and food is taken immediately in order to preserve the taste-masking. In case of mixture of the granules with solid foods or liquid it is important that it is taken immediately after mixing. Any unused medicinal product or waste material should be disposed of.

Nutritional management

Pheburane must be combined with dietary protein restriction and, in some cases, essential amino acid and carnitine supplementation.

Citrulline or arginine supplementation is required for patients diagnosed with the *neonatal-onset* form of carbamyl phosphate synthetase or ornithine transcarbamylase deficiency, at a dose of 0.17 g/kg/day or 3.8 g/m^2/day.

Arginine supplementation is required for patients diagnosed with deficiency of argininosuccinate synthetase, at a dose of 0.4 - 0.7 g/kg/day or 8.8 - 15.4 g/m^2/day.

If calorific supplementation is indicated, a protein-free product is recommended.

Therapeutic monitoring

Pheburane dosage should be adjusted according to the results of monitoring of plasma levels of ammonia, glutamine, serum protein and amino acids, and, where indicated, levels of phenylbutyrate and its metabolites).

Plasma levels of ammonia, arginine, essential amino acids (especially branched chain amino acids), carnitine and serum proteins should be maintained within normal limits. Plasma glutamine should be maintained at levels less than 1,000 µmol/L.

Administration

Pheburane should be administered orally. For patients unable to take the product orally, Pheburane may be administered by nasogastric or gastrostomy tube, as described below.

Administration by nasogastric or gastrostomy tube

Pheburane granules should not be administered by tube. A solution of Pheburane (50 mg/mL of sodium phenylbutyrate) must be prepared by hospital or pharmacy personnel

for administration through a nasogastric or gastrostomy tube according to the instructions below:

1. Weigh 51.75 g of Pheburane granules using a balance. One gram of Pheburane granules contains 0.483g of sodium phenylbutyrate so 51.75 g of Pheburane granules is equivalent to 25g of sodium phenylbutyrate.
2. Fill a 500 mL volumetric flask with about 400 mL of purified water; add a stir bar and start mixing on a magnetic stirrer;
3. Slowly pour Pheburane through a funnel into the volumetric flask; Maintain constant vigorous stirring for 60 minutes;
4. Remove the stir bar and make up to the 500 mL mark with purified water; Stopper the flask and invert once to mix;
5. Filter the solution through a stainless steel sieve (250 µm) and store in a sealed glass bottle. Protect from light with aluminum foil. Store in a refrigerator between 2°C to 8°C. Take the glass bottle from the refrigerator at least one (1) hour before use and shake vigorously prior to administration.

Note: the prepared solution provides 50 mg /mL of sodium phenylbutyrate and not the equivalent of 50 mg of Pheburane granules.

The appropriate volume of solution must be measured and administered with the use of a syringe directly through the nasogastric or gastrostomy tube and rinsed with water to clear the nasogastric or gastrostomy tube.

The solution of Pheburane should be used within 7 days when stored between 2°C to 8°C and protected from light.

Missed Dose

In the event a dose is missed, the dose should be taken as soon as possible, with the next meal. There should be at least 3 hours between two doses. The dose should not be doubled to make up for the missed doses.

4.3 CONTRAINDICATIONS

- Hypersensitivity to sodium phenylbutyrate or to any ingredient in the formulation;
- Pregnancy;
- Breastfeeding

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Pheburane should have therapy initiated and ongoing treatment supervised by a medical practitioner with expertise in the management of urea cycle disorders, as part of an individualised multidisciplinary approach.

Hyperammonia

Episodes of acute hyperammonemic encephalopathy may occur in patients even when they are on Pheburane therapy.

Pheburane is not recommended for the management of acute hyperammonemia, which is a life-threatening medical emergency that requires more rapidly acting interventions to reduce plasma ammonia levels.

Sodium content

Pheburane contains 124 mg (5.4 mmol) of sodium per gram of sodium phenylbutyrate, corresponding to 2.5 g (108 mmol) of sodium per 20 g of sodium phenylbutyrate (the maximum daily dose). Pheburane should be used with extreme caution, if at all, in patients with congestive heart failure or severe renal insufficiency, and with care in patients on a controlled sodium diet or in clinical conditions where there is sodium retention with edema.

Serum potassium levels

Serum potassium should be monitored during therapy since renal excretion of phenylacetylglutamine may induce urinary loss of potassium.

Sucrose content

Pheburane contains 768 mg of sucrose for each gram of sodium phenylbutyrate, corresponding to 15.4 g of sucrose in the maximum daily dose of 20 g of sodium phenylbutyrate. This should be considered in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Pheburane.

Neurologic

The major metabolite of sodium phenylbutyrate, phenylacetate, is associated with neurotoxicity. In a study of cancer patients administered phenylacetate intravenously, signs and symptoms of neurotoxicity were seen at plasma concentrations ≥ 3.5 mmol/l, including somnolence, fatigue, light headedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of pre-existing neuropathy. The adverse events were reversible upon discontinuation.

Serum drug levels of phenylbutyrate and its metabolites, phenylacetate and phenylglutamine, may be monitored periodically. In particular, plasma phenylacetate levels may be useful to guide dosing of Pheburane if symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or intercurrent illness.

Patient monitoring

Plasma levels of ammonia, arginine, essential amino acids (especially branched chain amino acids), carnitine and serum proteins should be maintained within normal limits. A fasting plasma ammonia level of less than half the age-adjusted upper limit of normal (ULN) has been used as a therapeutic target, and plasma glutamine should be maintained at levels less than 1,000 µmol/L. Urinalysis, blood chemistry profiles, and hematologic tests should be monitored routinely.

Use in Hepatic Impairment

Since sodium phenylbutyrate is metabolized in the liver and kidneys, Pheburane should

be used with caution in patients with hepatic insufficiency.

Use in Renal Impairment

Sodium phenylbutyrate is metabolized in the liver and kidneys to phenylacetylglutamine, which is primarily excreted by the kidneys. Pheburane should therefore be used with caution in patients with renal insufficiency (CrCl or eGFR < 60 mL/min).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Use in the elderly

Pheburane has not been studied in the geriatric population.

Paediatric use

PHEBURANE is recommended for infants (>1 month of age), children and adolescents based on the available clinical data.

Effects on laboratory tests

Interactions with laboratory tests have not been established.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug-Drug Interactions

No formal clinical drug-drug interaction studies have been performed with Pheburane. The drugs listed in Table 1 are based on potential pharmacologic interactions which may affect plasma ammonia levels; the potential interaction with probenecid is through pharmacokinetic interactions with sodium phenylbutyrate rather than a direct effect on the underlying metabolic disease.

Table 1- Potential Drug-Drug Interactions

Drug Proper Name	Reference	Clinical Comment
Probenecid	Theoretical	May inhibit renal excretion of sodium phenylbutyrate and phenylacetylglutamine.
Haloperidol	Case study	May induce hyperammonemia.
Valproate (or) Carbamazepine (or) Phenobarbital (or) Topiramate	Case study	May induce hyperammonemia.
Corticosteroids	Theoretical	May cause the breakdown of body protein and thus increase plasma ammonia levels.
Rifampicin	Case report	Hepatotoxicity after rifampicin ceased possibly due to reduction in CYP3A4 leading to toxic accumulation of phenylacetate.

More frequent monitoring of plasma ammonia levels is advised if the above-mentioned medicinal products must be used.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Dedicated fertility studies have not been conducted with sodium phenylbutyrate. A related substance, glycerol phenylbutyrate, had no effect on fertility or reproductive function in male and female rats dosed orally at up to 900 mg/kg/day (combined systemic exposure for phenylbutyrate and the active metabolite phenylacetate approximately 8 times that anticipated clinically with PHEBURANE). At doses of 1200 mg/kg/day, maternal toxicity was observed and the number of nonviable embryos was increased.

Amenorrhea/menstrual dysfunction was common in menstruating women administered sodium phenylbutyrate.

Use in pregnancy (Category B3)

The safety of this medicinal product for use in human pregnancy has not been established.

Exposure of rats to the active metabolite phenylacetic acid during pregnancy or early postnatal life was associated with reduced fetal brain weight, impaired performance in learning and memory tasks and neuroanatomical deficits. Reproductive toxicity studies have been conducted with glycerol phenylbutyrate, which is closely related to sodium phenylbutyrate. Oral administration of glycerol phenylbutyrate to rabbits at doses up to 350 mg/kg/day during the period of organogenesis had no effect on embryofetal development (combined systemic exposure for phenylbutyrate and the active metabolite phenylacetate approximately 2 times that anticipated clinically). In rats, no effects on embryofetal development were observed at oral doses of 300 mg/kg/day (combined systemic exposure for phenylbutyrate and phenylacetate approximately 4 times that anticipated clinically with PHEBURANE). Doses ≥ 650 mg/kg/day produced maternal toxicity and adverse effects on embryofetal development, including reduced fetal weights, skeletal variations and delayed ossification, and a wide range of non-specific malformations. No developmental abnormalities, effects on growth, or effects on learning and memory were observed in rats through day 92 post partum following oral administration of glycerol phenylbutyrate to pregnant rats at up to 900 mg/kg/day (combined systemic exposure for phenylbutyrate and the active metabolite phenylacetate approximately 8 times that anticipated clinically with PHEBURANE).

The significance of these data in pregnant women is not known; therefore the use of PHEBURANE is contra-indicated during pregnancy. **Effective contraceptive measures must be taken by women of child-bearing potential.**

Use in lactation

It is not known if phenylacetate is secreted in human milk, therefore the use of Pheburane is contraindicated during breastfeeding (see Section 4.3 CONTRAINDICATIONS).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Event Overview

The adverse events reported in the following section were derived from the published literature and the known safety profile of phenylbutyrate.

The most common clinical adverse event reported was amenorrhea/menstrual dysfunction (irregular menstrual cycles), which occurred in 23% of menstruating female patients. Decreased appetite occurred in 4% of patients. Body odour (probably caused by the metabolite, phenylacetate) and bad taste or taste aversion were each reported in 3% of patients.

Clinical Trial Adverse Events

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical adverse events were assessed in 183 urea cycle disorder patients treated with sodium phenylbutyrate in a published report of a long term Phase 3 clinical trial. Adverse events (clinical and laboratory) were not collected systematically, but were obtained from patient-visit reports by the co-investigators. Assessment of causality of adverse events was challenging in this population since the events may have resulted from either the underlying disease, the patient's restricted diet, intercurrent illness, or sodium phenylbutyrate. Furthermore, the rates may be under-estimated because they were

reported primarily by a parent or guardian and not the patient.

All adverse events are listed in Table 2 below by system organ class and by frequency. Frequency is defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

Table 2 – Summary of adverse events reported in clinical trials with sodium phenylbutyrate.

System Organ Class	Frequency	Adverse events
Blood and lymphatic system disorders	Common	anemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
	Uncommon	aplastic anemia, ecchymosis
Metabolism and nutrition disorders	Common	metabolic acidosis, alkalosis, decreased appetite
Psychiatric disorders	Common	depression, irritability
Nervous system disorders	Common	syncope, headache
	Common	oedema
	Uncommon	arrhythmia
Gastrointestinal disorders	Common	abdominal pain, vomiting, nausea, constipation, dysgeusia
	Uncommon	pancreatitis, peptic ulcer, rectal hemorrhage, gastritis
Skin and subcutaneous tissue disorders	Common	rash, abnormal skin odor
Renal and urinary disorders	Common	renal tubular acidosis
Reproductive system and breast disorders	Very common	amenorrhea, irregular menstruation

Investigations	Common	Decreased blood potassium, albumin, total protein and phosphate. Increased blood alkaline phosphatase, transaminases, bilirubin, uric acid, chloride, phosphate and sodium. Increased weight

Post-Marketing Adverse Events

The following adverse events have been reported during post-marketing surveillance: hyperammonaemia, ammonia increased, loss of consciousness, vomiting, urinary incontinence; abnormal faeces, choking, medication residue present and septic shock.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

In the event of an overdose, treatment with Pheburane should be discontinued and supportive measures instituted. Hemodialysis or peritoneal dialysis may be beneficial.

One case of overdose occurred in a 5-month old infant with an accidental single dose of 10 g (1370 mg/kg). The patient developed diarrhea, irritability and metabolic acidosis with hypokalaemia. The patient recovered within 48 hours after symptomatic treatment.

These symptoms are consistent with the accumulation of phenylacetate which showed dose-limiting neurotoxicity when administered intravenously at doses up to 400mg/kg/day. Manifestations of neurotoxicity were predominantly somnolence, fatigue,

and light-headedness. Less frequent manifestations were confusion, headache, dysgeusia, hypoacusis, disorientation, impaired memory and exacerbation of a pre-existing neuropathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX03.

Mechanism of action

Sodium phenylbutyrate is an ammonia scavenger. Sodium phenylbutyrate is a pro-drug and is rapidly metabolised to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine which is then excreted by the kidneys. On a molar basis, phenylacetylglutamine is comparable to urea (each containing 2 moles of nitrogen) and therefore provides an alternate vehicle for waste nitrogen excretion.

Based on studies of phenylacetylglutamine excretion in patients with urea cycle disorders, it is possible to estimate that, for each gram of sodium phenylbutyrate administered, between 0.12 and 0.15 g of phenylacetylglutamine nitrogen are produced. As a consequence, sodium phenylbutyrate reduces elevated plasma ammonia and glutamine levels in patients with urea cycle disorders. It is important that the diagnosis is made early and treatment is initiated immediately to improve the survival and the clinical outcome.

Clinical Trials

The efficacy of sodium phenylbutyrate in the treatment of urea cycle disorders was evaluated using the published clinical literature in this rare indication. In an open label, single arm, multicentre Phase 3 study of patients with deficiencies of carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinate synthetase (ASS). Efficacy results were evaluable for 183 patients enrolled across the United States and Canada over a period of more than 10 years. Efficacy criteria included survival, incidence of hyperammonemic episodes, cognitive development, growth, and plasma ammonia and glutamine levels.

Amongst *late-onset deficiency patients*, including females heterozygous for ornithine transcarbamylase deficiency, those who recovered from an episode of hyperammonemic encephalopathy and were then treated chronically with sodium phenylbutyrate and dietary protein restriction, the survival rate was 98%. The two deaths in this group of patients occurred during episodes of hyperammonaemic encephalopathy. However, compliance with the prescribed therapeutic regimen was not well documented, precluding evaluation of the potential for sodium phenylbutyrate and dietary protein restriction to prevent mental deterioration and recurrence of hyperammonaemic encephalopathy with optimal adherence. The majority of patients tested (30/46 or 65%) had IQ's in the average to low average/borderline mentally impaired range. Their cognitive performance remained relatively stable during phenylbutyrate therapy. Reversal of pre-existing neurologic impairment is considered unlikely to occur with treatment, and neurologic deterioration may continue in some patients, although cognitive performance remained relatively stable during phenylbutyrate therapy.

Even on therapy, acute hyperammonaemic encephalopathy recurred in the majority of patients for whom the drug was indicated.

Additional published studies (Lee et al., 2010, Diaz et al., 2011, Lichter-Konecki et al., 2011 and Smith et al., 2013) investigated a total of 85 patients (26 paediatric and 59 adult patients) with urea cycle disorders (UCDs). This total patient population included the following enzyme deficiency subtypes: OTC (n=64); ASS (n=8); CPS (n=2); argininosuccinate lyase (ASL) (n=9); arginase (ARG) (n=1) or hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH) (n=1).

In the short-term cross-over phases of these studies, sodium phenylbutyrate was used as the control arm to investigate non-inferiority of glycerol phenylbutyrate versus sodium phenylbutyrate. These studies provide further evidence of the clinical efficacy of sodium phenylbutyrate in UCD in terms of the clinical outcomes monitored in these studies.

Two meta-analyses of paediatric studies (Berry et al., 2014) or short-term paediatric and adult studies (Diaz et al., 2013) provide further confirmation of the efficacy of sodium phenylbutyrate in UCD.

Historical data

Historically, urea cycle disorders with a *neonatal-onset* were almost universally fatal within the first year after birth, despite treatment with peritoneal dialysis and essential amino acids, or their nitrogen-free analogs. However, with hemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate, and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in newborns diagnosed after birth but within the first month of life was almost 80%. Most deaths occurred during an episode of acute hyperammonemic encephalopathy. Patients with neonatal-onset disease had a high incidence of mental impairment. Those who had IQ tests administered had an incidence of mental impairment as follows: ornithine transcarbamylase deficiency, 100% (14/14 patients tested); argininosuccinic acid synthetase deficiency, 88% (15/17 patients tested); and carbamylphosphate synthetase deficiency, 57% (4/7 patients tested). Impairment was severe in the majority of the patients.

In patients diagnosed during gestation and treated prior to any episode of hyperammonemic encephalopathy, survival was 100%, but even in these patients, most subsequently demonstrated cognitive impairment or other neurologic deficits.

PHEBURANE may be required life-long unless orthotropic liver transplantation is elected.

5.2 PHARMACOKINETIC PROPERTIES

Phenylbutyrate is known to be oxidised to phenylacetate which is enzymatically conjugated with glutamine to form phenylacetylglutamine in the liver and kidney. Phenylacetate is also hydrolysed by esterases in liver and blood.

Plasma and urine concentrations of phenylbutyrate and its metabolites have been obtained from fasting normal adults who received a single dose of 5 g of sodium phenylbutyrate and from patients with urea cycle disorders, haemoglobinopathies and cirrhosis receiving single and repeated oral doses up to 20 g/day (uncontrolled studies). The disposition of phenylbutyrate and its metabolites has also been studied in cancer patients following intravenous infusion of sodium phenylbutyrate (up to 2 g/m^2) or phenylacetate.

Absorption

Phenylbutyrate is rapidly absorbed under fasting conditions. After a single oral dose of 5 g of sodium phenylbutyrate, in the form of granules, measurable plasma levels of phenylbutyrate were detected 15 minutes after dosing. The mean time to peak concentration was 1 hour and the mean peak concentration 195 µg/mL. The elimination half-life was estimated to be 0.8 hours.
The effect of food on absorption is unknown.

Distribution

The volume of distribution of phenylbutyrate is 0.2 l/kg.

Biotransformation

After a single dose of 5 g of sodium phenylbutyrate, in the form of granules, measurable plasma levels of phenylacetate and phenylacetylglutamine were detected 30 and 60 minutes respectively after dosing. The mean time to peak concentration was 3.55 and 3.23 hours, respectively, and the mean peak concentration was 45.3 and 62.8 µg/mL, respectively. The elimination half-life was estimated to be 1.3 and 2.4 hours, respectively.

Studies with high intravenous doses of phenylacetate showed non-linear pharmacokinetics characterised by saturable metabolism to phenylacetylglutamine. Repeated dosing with phenylacetate showed evidence of an induction of clearance.

In the majority of patients with urea cycle disorders or haemoglobinopathies receiving various doses of phenylbutyrate (300 - 650 mg/kg/day up to 20 g/day) no plasma level of phenylacetate could be detected after overnight fasting. In patients with impaired hepatic function the conversion of phenylacetate to phenylacetylglutamine may be relatively slower. Three cirrhotic patients (out of 6) who received repeated oral administration of sodium phenylbutyrate (20 g/day in three doses) showed sustained plasma levels of phenylacetate on the third day that were five times higher than those achieved after the first dose.

In normal volunteers gender differences were found in the pharmacokinetic parameters of phenylbutyrate and phenylacetate (AUC and Cmax about 30 - 50 %

greater in females), but not phenylacetylglutamine. This may be due to the lipophilicity of sodium phenylbutyrate and consequent differences in volume of distribution.

Excretion

Approximately 80 - 100 % of the medicinal product is excreted by the kidneys within 24 hours as the conjugated product, phenylacetylglutamine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Sodium phenylbutyrate was not genotoxic in the Ames test, in an in vitro chromosomal aberration assay in human lymphocytes or in an in vivo micronucleus assay in rats. Sodium phenylbutyrate metabolites phenylacetate (PAA) and phenylacetylglutamine (PAGN) were not genotoxic in the Ames test or in vitro chromosome aberration assay in Chinese hamster ovary cells.

Carcinogenicity

Carcinogenicity studies have not been conducted with sodium phenylbutyrate. In a rat study, the related substance, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma at a dose of 650 mg/kg/day in males (4 times the anticipated exposure in adult patients, based on combined AUCs for PBA and phenylacetate (PAA) and 900 mg/kg/day in females (9 times the anticipated exposure in adult patients, based on combined AUCs for PBA and PAA). The incidence of the following tumors was also increased in female rats at a dose of 900 mg/kg/day: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, uterine endometrial stromal polyp, and combined polyp or sarcoma. Glycerol phenylbutyrate was not tumourigenic in a 26-week transgenic mouse study.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ethylcellulose

Hypromellose

macrogol 1500

maize starch

povidone

Suglets sugar spheres 250/355 micrometres (ARPING 12751)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this product

6.3 SHELF LIFE

Pheburane granules:

Store below 30°C. Protect from light.
Shelf life: 3 years. After the first opening, Pheburane should be used within 45 days.

Pheburane solution for nasogastric or gastrostomy administration:

Store between 2°C to 8°C. Protect from light.
After preparation, Pheburane solution (50 mg/mL of sodium phenylbutyrate) should be used within 7 days.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE bottle, child-resistant closure with desiccant, containing 174 g of granules. Each carton contains one bottle.

A calibrated measuring spoon is provided.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In case of mixture of the granules with solid foods or liquid it is important that it is taken immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

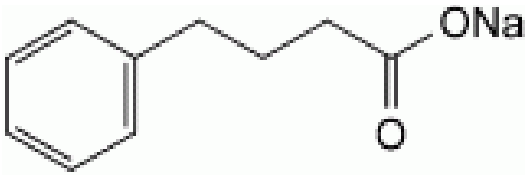
6.7 PHYSICOCHEMICAL PROPERTIES

Sodium 4-phenylbutanoate

Molecular Formula: $C_{10}H_{11}NaO_2$

Molecular weight: 186.2

Chemical structure



CAS number

104206-65-7

The active substance is a white or yellowish-white powder and freely soluble in water and in methanol, practically insoluble in methylene chloride. Its pKa is 4.76 and log P is 2.42.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8. SPONSOR

Orpharma Pty Ltd

Level 1, 1 Queens Road

Melbourne

Victoria 3004

Orpharma Medical Information phone number: 1800 290 930

Email: medical@orpharma.com

www.orpharma.com

9. DATE OF FIRST APPROVAL

30/05/2017

10. DATE OF REVISION OF THE TEXT

05/03/2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All PI	Updated to new format