NEW ZEALAND DATA SHEET –

PHEBURANE™ sodium phenylbutyrate granules

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1. PRODUCT NAME

PHEBURANE 483 mg/g granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Granules.

White to off-white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pheburane is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase. 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).

Pheburane is indicated in all patients with *neonatal-onset* presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

Geriatrics (> 65 years of age):
Pheburane has not been studied in the geriatric population.

4.2 Dose and method of administration

Dosing Considerations
Pheburane treatment should be supervised by a health professional experienced in the treatment of urea cycle disorders.
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.

Dose
The usual total daily dose of sodium phenylbutyrate is:
450 - 600 mg/kg/day in neonates, infants and children weighing less than 20 kg;
9.9 - 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.

Recommended doses for oral administration of Pheburane granules are shown in Table 1 and Table 2.

Table 1- Recommended doses of Pheburane granules (expressed in mg of sodium phenylbutyrate) for oral dosing in neonates, infants and children weighing less than 20 kg

Weight (kg)	Dosing interval	
	Minimum dose (mg) per day	Maximum dose (mg) per day
3	1350	1800
4	1800	2400
5	2250	3000
7.5	3375	4500
10	4500	6000
15	6750	9000
20	9000	12000

Table 2- Recommended doses of Pheburane granules (expressed in grams of sodium phenylbutyrate) for oral dosing in children weighing more than 20 kg, adolescents and adults

Body Surface Area (m^2)	Dosing interval	
	Minimum dose (g) per day	Maximum dose (g) per day
0.8	7.9	10.4
1.05	10.4	13.7
1.27	12.6	16.5
1.48	14.7	19.2
1.66	16.4	20.0*
1.84	18.2	20.0*
1.97	19.5	20.0*

*The safety and efficacy of doses in excess of 20 g/day have not been established.

Recommended doses for administration of Pheburane solution through nasogastric or gastrostomy tube are shown in Table 3 and Table 4.

Table 3- Recommended doses of Pheburane solution (50 mg/ml of sodium phenylbutyrate) prepared for administration by nasogastric or gastrostomy tube in neonates, infants and children weighing less than 20 kg

Weight (kg)	Dosing interval	
	Minimum dose (ml) per day	Maximum dose (ml) per day
3	27.0	36.0
4	36.0	48.0
5	45.0	60.0
7.5	67.5	90.0
10	90.0	120.0
15	135.0	180.0
20	180.0	240.0

Table 4- Recommended doses of Pheburane solution (50 mg/ml of sodium phenylbutyrate) prepared for administration by nasogastric or gastrostomy tube in children weighing more than 20 kg, adolescents and adults

Body Surface Area (m^2)	Dosing interval	
	Minimum dose (ml) per day	Maximum dose (ml) per day
0.8	158.4	208.0
1.05	207.9	273.0
1.27	251.5	330.2
1.48	293.0	384.8
1.66	328.7	400.0*
1.84	364.3	400.0*
1.97	390.1	400.0*

*The safety and efficacy of doses in excess of 20 g/day have not been established.

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 (see section 4.4 Special warnings and precautions of use, Monitoring and Laboratory Tests).

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 caloric supplementation is indicated, a protein-free product is recommended.

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.

Method of administration

Pheburane should be administered orally. For patients unable to take the product orally, Pheburane may be administered by nasogastric or gastrostomy tube (see section 6.6 Special precautions for disposal <and other handling>, Administration by nasogastric or gastrostomy tube).

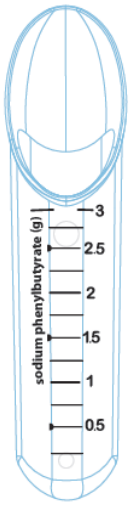
Oral administration

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.

A calibrated dosing spoon is provided which dispenses up to 3 g of sodium phenylbutyrate, in graduations of 250 mg. Only use the dosing spoon provided with the medicine to measure out the dose.

Table 7- How to use the calibrated dosing spoon*

Prescribed quantity of sodium phenylbutyrate per dose (g)	How to use the calibrated dosing spoon
0.25 g	Pour the granules directly into the spoon up until the first (1st) black line, from the bottom of the scale, representing 0.25 g of sodium phenylbutyrate
0.5 g	Pour the granules directly into the spoon up until the second (2nd) black line, representing 0.5 g of sodium phenylbutyrate
1g	Pour the granules directly into the spoon up until the fourth (4th) black line, representing 1 g of sodium phenylbutyrate
1.5 g	Pour the granules directly into the spoon up until the sixth (6th) black line, representing 1.5 g of sodium phenylbutyrate
2g	Pour the granules directly into the spoon up until the eighth (8th) black line, representing 2 g of sodium phenylbutyrate
3g	Pour the granules directly into the spoon up until the twelfth (12th) black line, representing 3 g of sodium phenylbutyrate



For Administration by nasogastric or gastrostomy tube, please see section 6.6 Special precautions for disposal <and other handling>.

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

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.

Hepatic

Since sodium phenylbutyrate is metabolized in the liver and kidneys, Pheburane should be used with caution in patients with hepatic insufficiency (see (see section 4.4 Special warnings and precautions of use, Monitoring and Laboratory Tests).

Renal

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 (see section 4.4 Special warnings and precautions of use, Monitoring and Laboratory Tests).

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.

If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia levels or other intercurrent illnesses, consider reducing the dose of Pheburane, and assessment of plasma phenylacetate level may be useful (see section 4.4 Special warnings and precautions of use, Monitoring and Laboratory Tests).

Special Populations

Geriatrics (> 65 years of age): Pheburane has not been studied in the geriatric population.

Paediatric population: Pheburane has not been studied in the paediatric population.

Monitoring and Laboratory Tests

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.

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 if symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or intercurrent illness.

4.5 Interaction with other medicines and other forms of interaction

Drug-Drug Interactions

No formal clinical drug-drug interaction studies have been performed with Pheburane. The drugs listed in Table 5 are based on potential pharmacologic interactions which may affect plasma ammonia levels.

Table 5- 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.

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.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established. Animal studies have shown adverse effects on the fetus (see Preclinical safety data). Because the significance of these data in pregnant women is not known, the use of Pheburane is contraindicated during pregnancy (see 4.3 Contraindications). **Effective contraceptive measures must be taken by women of child-bearing potential.**

Breast-feeding

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

Fertility

The effect of sodium phenylbutyrate on fertility in humans is unknown. Amenorrhea/menstrual dysfunction was common in menstruating women administered sodium phenylbutyrate (see 4.8 Undesirable effects).

4.7 Effects on ability to drive and use machines

The effects of Pheburane on the ability to drive and operate machines have not been

established.

4.8 Undesirable effects

Adverse Drug Reaction Overview

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 odor (probably caused by the metabolite, phenylacetate) and bad taste or taste aversion were each reported in 3% of patients.

Clinical Trial Adverse Drug Reactions

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 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 reactions are listed in Table 6 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 reactions are presented in order of decreasing seriousness.

Table 6 – Summary of adverse drug reactions reported in clinical trials with sodium phenylbutyrate.

System Organ Class	Frequency	Adverse reaction
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

Cardiac disorders	Common Uncommon	odema arrhythmia
Gastrointestinal disorders	Common Uncommon	abdominal pain, vomiting, nausea, constipation, dysgeusia 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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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.

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 and pharmacodynamic effects
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.

Clinical efficacy and safety
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.

In *late-onset deficiency* patients, including females heterozygous for ornithine transcarbamylase deficiency, who recovered from hyperammonaemic encephalopathy and were then treated chronically with dietary protein restriction and sodium phenylbutyrate, the survival rate was 98%. The majority of the patients who were tested had an IQ in the average to low average/borderline mentally retarded range. Their cognitive performance remained relatively stable during phenylbutyrate therapy. Reversal of pre-existing neurologic impairment is not likely to occur with treatment, and neurologic deterioration may continue in some patients.

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

Paediatric population
Previously, *neonatal-onset* presentation of urea cycle disorders was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their nitrogen-free analogues. With haemodialysis, 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) increased to almost 80% with most deaths occurring during an episode of acute hyperammonaemic encephalopathy. Patients with *neonatal-onset* disease had a high incidence of mental retardation.

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

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 C_{max} 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

Single-dose toxicity
No single-dose toxicity studies have been performed for sodium phenylbutyrate. However, in a genotoxicity study (micronucleus test), rats received a single oral dose of sodium phenylbutyrate (878, 1568 or 2800 mg/kg) and deaths were observed at both of the higher doses: 7/10 at 2800 mg/kg and 2/10 at 1568 mg/kg.

Repeated-dose toxicity
No repeat-dose toxicity studies have been performed for sodium phenylbutyrate.

Parenteral administration of phenylacetate in young rats had harmful effects on brain development. When high doses of phenylacetate (190 - 474 mg/kg), the active metabolite of phenylbutyrate, were given subcutaneously to rat pups, decreased proliferation and increased loss of neurons were observed, as well as a reduction in central nervous system CNS myelin. Cerebral synapse maturation was retarded and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth.

Carcinogenicity
The carcinogenic potential of sodium phenylbutyrate has not been studied.

Mutagenesis
Sodium phenylbutyrate was negative in 2 mutagenicity tests: the Ames test and the micronucleus test. Sodium phenylbutyrate did not induce mutagenic effects in the Ames test, with or without metabolic activation. In the micronucleus test sodium phenylbutyrate did not produce clastogenic effects in rats treated at toxic or non-toxic doses, examined 24 and 48 hours after oral administration of single doses of 878 to 2800 mg/kg.

Reproduction
Dedicated fertility studies have not been conducted with sodium phenylbutyrate. However, animal studies have shown reproductive toxicity of sodium phenylbutyrate, i.e. effects on the development of the embryo or the fetus. Prenatal exposure of rat pups to phenylacetate (the active metabolite of phenylbutyrate) produced lesions in cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylcellulose N7
Hydroxypropylmethylcellulose
Macrogol 1500
Maize starch
Povidone K25 and sucrose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Pheburane granules:
3 years.
Store at room temperature (15 to 30°C).
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

Not applicable.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

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 <and other handling>

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.

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:

- Weigh 51.75 g of Pheburane;
- Fill a 500 ml volumetric flask with about 400 ml of purified water; add a stir bar and start mixing on a magnetic stirrer;
- Slowly pour Pheburane through a funnel into the volumetric flask; Maintain constant vigorous (approximately 350 rpm) stirring for 60 minutes;
- Remove the stir bar and make up to the 500 ml mark with purified water;
- Stopper the flask and turn once to mix;
- 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.

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.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Orpharma NZ Limited
c/o Staples Rodway Limited
Level 9, 45 Queen Street
P O Box 3899
Auckland 1140

9. DATE OF FIRST APPROVAL

29/10/2015

10. DATE OF REVISION OF THE TEXT

27/03/2019

SUMMARY TABLE OF CHANGES

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