1. NAME OF THE MEDICINAL PRODUCT

PHEBURANE®

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.
It 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.

4.2 Posology and method of administration

PHEBURANE treatment should be supervised by a physician experienced in the treatment of urea cycle disorders.

Posology
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.

The usual total daily dose of sodium phenylbutyrate in clinical experience 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 of sodium phenylbutyrate have not been established.

Therapeutic monitoring
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.

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 *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.

Special populations
Renal and hepatic impairment
Since the metabolism and excretion of sodium phenylbutyrate involves the liver and kidneys, PHEBURANE should be used with caution in patients with hepatic or renal insufficiency.

Method of administration
PHEBURANE should be administered orally. Because of its slow dissolution, PHEBURANE should not be administered by nasogastric or gastrostomy tubes.

The total daily dose 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 foods (mashed potatoes or apple sauce); in this case, it is important that it is taken immediately in order to preserve the taste-masking.

The dose of PHEBURANE is expressed in grams of sodium phenylbutyrate. A calibrated measuring spoon is provided. It dispenses up to 3g of sodium phenylbutyrate by graduation of 250 mg.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy.
- Breast-feeding.

4.4 Special warnings and precautions for use

Content of clinically important electrolytes
- 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, which is the maximum daily dose. PHEBURANE should therefore be used with caution in patients with congestive heart failure or severe renal insufficiency, and in clinical conditions where there is sodium retention with oedema.
- Serum potassium should be monitored during therapy since renal excretion of phenylacetylglutamine may induce a urinary loss of potassium.

General considerations
- Even on therapy, acute hyperammonaemic encephalopathy may occur in a number of patients.
- PHEBURANE is not recommended for the management of acute hyperammonaemia, which is a medical emergency.

Excipients with known effect
- This medicinal product contains 124 mg sodium per gram of sodium phenylbutyrate, equivalent to 6.2% of the WHO recommended maximum daily intake for sodium. The

maximum daily dose of this medicinal product is equivalent to 125% of the WHO recommended maximum daily intake for sodium.

- PHEBURANE is considered high in sodium. This should be particularly taken into account for those on a law salt diet.
- This medicinal product contains 768 mg sucrose per gram of sodium phenylbutyrate. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of probenecid may affect renal excretion of the conjugation product of sodium phenylbutyrate. There have been published reports of hyperammonaemia being induced by haloperidol and by valproate. Corticosteroids may cause the breakdown of body protein and thus increase plasma ammonia levels. More frequent monitoring of plasma ammonia levels is advised when these medicinal products have to be used.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Effective contraceptive measures must be taken by women of child-bearing potential.

Pregnancy
There are no or limited amount of data from the use of sodium phenylbutyrate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). PHEBURANE is contra-indicated during pregnancy (see section 4.3). Women of childbearing potential must use effective contraception during treatment.

Breast-feeding
Available pharmacodynamic/toxicological data in animals have shown excretion of sodium phenylbutyrate/metabolites in milk (see section 5.3). It is unknown whether sodium phenylbutyrate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. PHEBURANE is contra-indicated during breast-feeding (see section 4.3).

Fertility
There is no evidence available on the effect of sodium phenylbutyrate on fertility.

4.7 Effects on ability to drive and use machines

PHEBURANE has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile
In clinical trials with sodium phenylbutyrate, 56 % of the patients experienced at least one adverse event and 78 % of these adverse events were considered as not related to sodium phenylbutyrate.
Adverse reactions mainly involved the reproductive and gastrointestinal system.

Tabulated list of adverse reactions
In the table below all adverse reactions are listed 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.

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	anaemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
	Uncommon	aplastic anaemia, 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	oedema
	Uncommon	arrhythmia
Gastrointestinal disorders	Common	abdominal pain, vomiting, nausea, constipation, dysgeusia
	Uncommon	pancreatitis, peptic ulcer, rectal haemorrhage, 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

Description of selected adverse reactions
A probable case of toxic reaction to sodium phenylbutyrate (450 mg/kg/d) was reported in an 18-year-old anorectic female patient who developed a metabolic encephalopathy associated with lactic acidosis, severe hypokalaemia, pancytopaenia, peripheral neuropathy, and pancreatitis. She recovered following dose reduction except for recurrent pancreatitis episodes that eventually prompted treatment discontinuation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

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 400 mg/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.
In the event of an overdose, the treatment should be discontinued and supportive measures be instituted. Haemodialysis or peritoneal dialysis may be beneficial.

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/m²) 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

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 (see section 4.6).
When high doses of phenylacetate (190 - 474 mg/kg) were given subcutaneously to rat pups, decreased proliferation and increased loss of neurons were observed, as well as a reduction in 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. (see section 4.6).
Sodium phenylbutyrate was negative in 2 mutagenicity tests, i.e. the Ames test and the micronucleus test. Results indicate that sodium phenylbutyrate did not induce any mutagenic effects in the Ames test with or without metabolic activation. Micronucleus test results indicate that sodium phenylbutyrate was considered not to have produced any clastogenic effect in rats treated at toxic or non-toxic dose levels (examined 24 and 48 hours after a single oral administration of 878 to 2800 mg/kg).

Carcinogenicity and fertility studies have not been conducted with sodium phenylbutyrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sugar spheres 250-355,
hypromellose,
ethylcellulose N7,
macrogol 1500,
povidone K25.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After the first opening, to be used within 45 days.

6.4 Special precautions for storage

Do not store above 25°C.

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 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.

7. MANUFACTURER

Eurocept International BV
Trapgans 5 1244 RL Ankeveen, The Netherlands

8. REGISTRATION HOLDER

Truemed Ltd.
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9. REGISTRATION NUMBER

153-57-34275

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