ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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.

It is indicated in all patients with *neonatal-onset* disease (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 (5.4 mmol) sodium per gram granules, equivalent to 6.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
  The maximum daily dose of this medicinal product contains 2.5 g sodium per 20 gram granules, equivalent to 125% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
  PHEBURANE is considered high in sodium. This should be particularly taken into account for those on a low salt diet.
- This medicinal product contains 768 mg sucrose per gram granules. 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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/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 mcg/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 (sucrose and maize starch)
Hypromellose
Ethylcellulose
Macrogol 1500
Povidone K25

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After the first opening, to be used within 45 days.

6.4 Special precautions for storage

Not applicable.

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. MARKETING AUTHORISATION HOLDER

Eurocept International BV
Trapgans 5
1244 RL Ankeveen
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/822/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013
Date of latest renewal: 21 March 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

PHEBURANE 350 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains 350 mg of sodium phenylbutyrate.

Excipient(s) with known effect

PHEBURANE 350 mg/mL oral solution
Each gram dose of sodium phenylbutyrate contains 5.7 mg of aspartame and 124 mg (5.4 mmol) of sodium.

Blackcurrant flavour topping
Each drop of blackcurrant flavour topping contains 26.55 mg of propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, colourless to pale yellow liquid.

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* disease (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 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.

Paediatric population
The usual total daily dose of sodium phenylbutyrate in paediatric patients in clinical experience is:
- 450 - 600 mg/kg/day in neonates, infants and children weighing less than 20 kg.
- 9.9 - 13 g/m^2/day in children weighing more than 20 kg.

Method of administration

PHEBURANE oral solution is for oral use.

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).

A dosing syringe with a press in bottle adapter (PIBA) is provided for accurate measurement of the prescribed dose of the oral solution. The PIBA allows to connect the dosing syringe to the bottle and to dose PHEBURANE oral solution.

Only the dosing syringe provided with PHEBURANE oral solution should be used to measure a dose of PHEBURANE oral solution. No other devices/spoons/syringes should be used to administer PHEBURANE oral solution.

The syringe is graduated in grams of sodium phenylbutyrate (from 0.5 g to 3 g of sodium phenylbutyrate.

PHEBURANE oral solution can also be administered by nasogastric or gastrostomy tubes.

Instructions for oral administration and administration via nasogastric or gastrostomy tube are provided in section 6.6.

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

- Each gram of PHEBURANE oral solution (2.86 mL of PHEBURANE oral solution) contains 124 mg (5.4 mmol) of sodium. The maximum daily dose of sodium phenylbutyrate is 20 g (57.14 mL of PHEBURANE oral solution), this would bring an associated amount of: 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 oral solution is not recommended for the management of acute hyperammonaemia, which is a medical emergency.

Excipients with known effect

PHEBURANE 350 mg/mL oral solution

- This medicinal product contains 124 mg (5.4 mmol) sodium per g dose of sodium phenylbutyrate, equivalent to 6.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
  The maximum daily dose of this medicinal product contains 2.5 g sodium , equivalent to 125% of the WHO recommended maximum daily intake of 2 g of sodium for an adult. PHEBURANE oral solution is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

- This medicinal product contains 5.7 mg aspartame per g dose of sodium phenylbutyrate. Aspartame is a source of phenylalanine. It may be harmful for persons who have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly. Neither non-clinical nor clinical data are available to assess aspartame (E951) use in infants below 12 weeks of age.

Blackcurrant flavour topping
The blackcurrant flavour topping contains 26.55 mg propylene glycol per drop.

If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

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 door
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/day) 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

One case of overdose occurred in a 5-month old infant with an accidental single dose of 10 g (1,370 mg/kg). The patient developed diarrhoea, 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 oral solution 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. Under fed conditions in the single-dose, open, pharmacokinetic study (CPA 537-21), after a single oral dose of 5 g of sodium phenylbutyrate, in the form of oral solution, measurable plasma levels of phenylbutyrate were detected 10 minutes after dosing. The mean time to peak concentration was 0.5 hour and the mean peak concentration 150.44 µg/ml. The elimination half-life was estimated to be 0.63 hours.

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

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

Oral solution

Purified water
Aspartame (E951)
Sucralose
Glycerol
Hydroxyethylcellulose

Flavour toppings

Blackcurrant flavour topping
Blackcurrant and mint flavouring, contains propylene glycol (E1520).

Lemon-mint flavour topping
Lemon and mint flavouring.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Oral solution

Unopened bottle: 3 years
After first opening: 4 weeks

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottle containing 100 mL closed with a plastic child-resistant cap.

Each pack contains:
- One amber glass bottle containing 100 mL PHEBURANE oral solution,
- One amber glass bottle containing 3 mL of lemon-mint flavour topping.
- One amber glass bottle containing 3 mL of blackcurrant flavour topping.
- One dosing syringe ranging from 0.5 g to 3 g with 0.25 increments with attached bottle adapter (PIBA).The graduation of the dosing syringe reflects the grams of sodium phenylbutyrate.

6.6 Special precautions for disposal and other handling

The oral solution of PHEBURANE is ready-to use.

Administration for oral use

1. The bottle of PHEBURANE oral solution should be opened by pushing down on the cap and twisting it to the left;
2. The CE marked dosing syringe is attached to the bottle adapter;
3. The bottle adapter should be placed/pushed into the neck of the open bottle while the syringe is in it;
4. The bottle should be inverted;
5. The required dose of PHEBURANE (see section 4.2) should be taken from the bottle (equivalent to the number of grams sodium phenylbutyrate as prescribed and according to the amount to be given with the respective meal) with the use of the dosing syringe;
6. The dosing syringe with PHEBURANE should be detached from the bottle adapter and the quantity of PHEBURANE oral solution should then be poured from the dosing syringe into a glass with minimum 20 ml of water;
7. PHEBURANE oral solution tastes neutral. In order to improve the taste, one drop of the preferred flavour topping can be added to the content of the glass of water; swirled gently, and then consumed (If one drop of flavour topping would not provide the taste intensity, patient could use 2 drops);
8. The bottle with PHEBURANE oral solution should be closed, without removing the bottle adapter inserted in the neck of the bottle.

Preparation for nasogastric tube or gastrostomy tube administration

PHEBURANE oral solution can be administered with tubes of a diameter of 2 mm (7-8 French) and larger.

In patients who have to receive sodium phenylbutyrate, permanently or at certain times during daytime (e.g. at night) via a nasogastric tube or gastrostomy tube/button, these routes may be used to administer PHEBURANE oral solution following the instructions below:

1. Steps 1 to 5 of the administration for oral use above should be followed;
2. The oral solution of PHEBURANE is ready-to use and no dilution is needed;
3. When used via nasogastic/gastrostomy tube the flavour topping should not be added;
4. The tip of the syringe filled with the medicinal product should be inserted onto the tip of the nasogastric/gastrostomy tube;
5. The plunger of the dosing syringe to administer the dose of PHEBURANE oral solution into the nasogastric/gastrostomy tube should be used;
6. The tube should be flushed once with the adequate volume of lukewarm water and allowed to drain after the administration. For adults, 20 ml of lukewarm water should be used. For children weighing less than 20 kg and neonates use 3 mL of water.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Eurocept International BV
Trapgans 5
1244 RL Ankeveen
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/822/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2013
Date of latest renewal: 21 March 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Eurocept International BV
Trapgans 5
1244 RL Ankeveen
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

PHEBURANE 483 mg/g granules
sodium phenylbutyrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gram of granules contains 483 mg of sodium phenylbutyrate

3. LIST OF EXCIPIENTS

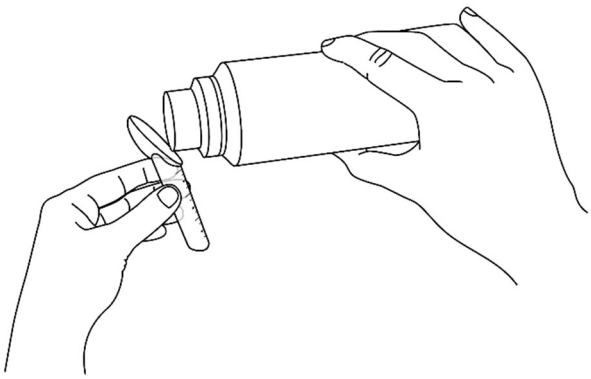
Contains sodium and sucrose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules
Carton: One bottle with 174 g granules.
Bottle: 174 g granules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Only use the calibrated measuring spoon provided.



6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After the first opening, to be used within 45 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eurocept International BV (Lucane Pharma)
Trapgans 5
1244 RL Ankeveen
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/822/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PHEBURANE 483 mg/g {For carton only}

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL 100 mL

1. NAME OF THE MEDICINAL PRODUCT

PHEBURANE 350 mg/mL oral solution
sodium phenylbutyrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains 350 mg of sodium phenylbutyrate

3. LIST OF EXCIPIENTS

Contains aspartame and sodium.
Carton: The blackcurrant flavour topping contains propylene glycol
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

Carton

One bottle with 100 mL oral solution
One bottle with 3 mL lemon-mint flavour topping
One bottle with 3 mL blackcurrant flavour topping
One dosing syringe + bottle adapter

Bottle label

100 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Only use the dosing syringe provided.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8 EXPIRY DATE

EXP
Discard 4 weeks after first opening.

9 SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eurocept International BV (Lucane Pharma)
Trapgans 5
1244 RL Ankeveen
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/822/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Carton:
PHEBURANE 350 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC

SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL FOR BLACKURRANT FLAVOR TOPPING

1. NAME OF THE MEDICINAL PRODUCT

Blackcurrant flavour topping for Pheburane 350 mg/ml oral solution

2. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

3. EXPIRY DATE

EXP
Discard 4 weeks after first opening.

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

Contains E1520

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL FOR LEMON-MINT FLAVOR TOPPING

1. NAME OF THE MEDICINAL PRODUCT

Lemon-mint flavour topping for Pheburane 350 mg/ml oral solution

2. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

3. EXPIRY DATE

EXP
Discard 4 weeks after first opening.

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

PHEBURANE 483 mg/g granules
Sodium phenylbutyrate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What PHEBURANE is and what it is used for

PHEBURANE contains the active substance sodium phenylbutyrate which is used to treat patients of all ages with urea cycle disorders. These rare disorders are due to a deficiency of certain liver enzymes which are necessary to eliminate waste nitrogen in the form of ammonia.

Nitrogen is a building block of proteins, which are an essential part of the food we eat. As the body breaks down protein after eating, waste nitrogen, in the form of ammonia, accumulates because the body cannot eliminate it. Ammonia is especially toxic for the brain and leads, in severe cases, to reduced levels of consciousness and to coma.

This medicine helps the body to eliminate waste nitrogen, reducing the amount of ammonia in your body. However PHEBURANE must be used along with a diet reduced in proteins, designed especially for you by the doctor and the dietician. You must follow this diet carefully.

2. What you need to know before you take PHEBURANE

Do not take PHEBURANE if you:
- are allergic to sodium phenylbutyrate or any of the other ingredients of this medicine (listed in section 6).
- are pregnant.
- are breast-feeding.

Warnings and precautions
Talk to your doctor or pharmacist before taking PHEBURANE if you:
- suffer from congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body) or a decrease in your kidney function.
- have decreased kidney or liver function, since PHEBURANE is eliminated from the body through the kidney and liver.

PHEBURANE will not prevent the occurrence of an acute excess of ammonia in the blood, a condition which usually constitutes a medical emergency. If this happens you will develop symptoms such as feeling sick (nausea), being sick (vomiting), confusion and will need to get urgent medical help.

If you need laboratory tests, it is important to remind your doctor that you are taking PHEBURANE, since sodium phenylbutyrate may interfere with certain laboratory test results (such as blood electrolytes or protein, or liver function tests)

In case of any doubt, ask your doctor or pharmacist.

Other medicines and PHEBURANE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is especially important to tell your doctor if you are taking medicines containing:
- valproate (an antiepileptic medicine).
- haloperidol (used in certain psychotic disorders).
- corticosteroids (medicines that are used to provide relief for inflamed areas of the body),
- probenecid (for treatment of hyperuricaemia, high levels of uric acid in the blood, associated with gout).

These medicines may change the effect of PHEBURANE and you will need more frequent blood tests. If you are uncertain if your medicines contain these substances, you should check with your doctor or pharmacist.

Pregnancy and breast-feeding
Do not use PHEBURANE if you are pregnant, because this medicine can harm your unborn baby.

If you are a woman who could get pregnant, **you must use reliable contraception, during treatment with PHEBURANE**. Talk to your doctor for the details.

Do not use PHEBURANE if you are breast-feeding, because this medicine can pass into the breast milk and may harm your baby.

Driving and using machines
PHEBURANE is unlikely to affect your ability to drive and use machines.

PHEBURANE contains sodium and sucrose
This medicine contains 124 mg (5.4 mmol) sodium (main component of cooking/table salt) in each gram granules. This is equivalent to 6,2% of the recommended maximum daily dietary intake of sodium for an adult.
The maximum daily dose of this medicine contains 2.5 mg sodium per 20 gram granules. This is equivalent to 125% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor or pharmacist if you need 3 or more grams daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

This medicine contains 768 mg sucrose in each gram granules. This should be taken into account if you have diabetes mellitus. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take PHEBURANE

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dose
The daily dose of PHEBURANE will be based on your body weight or body surface and adjusted according to your protein tolerance and diet. You will need regular blood tests to determine the correct daily dose. Your doctor will tell you the amount of granules you should take.

Method of administration
You should take PHEBURANE by mouth. Because it dissolves slowly, PHEBURANE should not be administered through a gastrostomy (tube that goes through the abdomen to the stomach) or through a nasogastric tube (tube that goes through the nose to the stomach).

PHEBURANE must be taken with a special diet reduced in protein.

You should take PHEBURANE with each meal or feeding. In small children this can be 4 to 6 times per day.

The doses of PHEBURANE prescribed by your doctor are expressed in grams of sodium phenylbutyrate. A calibrated measuring spoon which dispenses up to 3 g of sodium phenylbutyrate at a time is provided with the medicine. Only use this measuring spoon to measure out the dose of PHEBURANE. The measuring spoon must not be used for any other medicine.

To measure the dose:
- Lines on the spoon indicate the amount of PHEBURANE in gram of sodium phenylbutyrate. Take the correct amount as prescribed by your doctor.
- Pour granules directly into the spoon as shown by the picture (on the outer carton and in this leaflet).
- Tap the spoon once on a table to give a horizontal level of granules and continue filling if necessary.

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). If you mix them with food, it is important that you take it immediately. This will keep the granules from producing any taste.

You will need to take this medicine and to follow a diet throughout your life.

If you take more PHEBURANE than you should
Patients who have taken very high doses of sodium phenylbutyrate experienced:
- sleepiness, tiredness, light-headedness and less frequently confusion;
- headache;
- changes in taste (taste disturbances);
- decrease in hearing;
- disorientation;
- impaired memory;
- worsening of existing neurological conditions.

If you experience any of these symptoms, you should immediately contact your doctor or the nearest hospital emergency department for supportive treatment.

If you forget to take PHEBURANE

You should take a dose as soon as possible with your next meal. Make sure that there are at least 3 hours between two doses. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If persistent vomiting occurs, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people): irregular menstrual periods and stopping of menstrual periods in fertile women.
If you are sexually active and your period stops altogether, do not assume that this is caused by PHEBURANE. If this occurs, please discuss it with your doctor, because the absence of your period may be caused by pregnancy (see 'Pregnancy and breast-feeding' section above) or by menopause.

Common side effects (may affect more than 1 in 100 people): changes in number of blood cells (red cells, white cells and platelets), changes in the amount of bicarbonate in the blood, reduced appetite, depression, irritability, headache, fainting, fluid retention (swelling), changes in taste (taste disturbances), stomach ache, vomiting, nausea, constipation, abnormal skin odour, rash, abnormal kidney function, weight gain, altered laboratory test values.

Uncommon side effects (may affect more than 1 in 1,000 people): deficiency in red blood cells due to failure of the bone marrow, bruising, altered heart rhythm, rectal bleeding, inflammation of the stomach, stomach ulcer, inflammation of the pancreas.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PHEBURANE

Keep this medicine out of the sight and reach of children.

Do not use PHEBURANE after the expiry date which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.

After the first opening, PHEBURANE can be used within 45 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PHEBURANE contains
The active substance is sodium phenylbutyrate.
Each gram of granules contains 483 mg of sodium phenylbutyrate.
The other ingredients are: sugar spheres (sucrose and maize starch, see section 2 'PHEBURANE contains sucrose), hypromellose, ethylcellulose N7, macrogol 1500, povidone K25.

What PHEBURANE looks like and contents of the pack
PHEBURANE granules are white to off-white.

The granules are packaged in a plastic bottle with child-resistant closure and a dessicant.
Each bottle contains 174g of granules.

Each carton contains 1 bottle.

A calibrating measuring spoon is provided.

Marketing Authorisation Holder
Eurocept International BV
Trapgans 5
1244 RL Ankeveen
The Netherlands

Manufacturer
Eurocept International BV
Trapgans 5
1244 RL Ankeveen
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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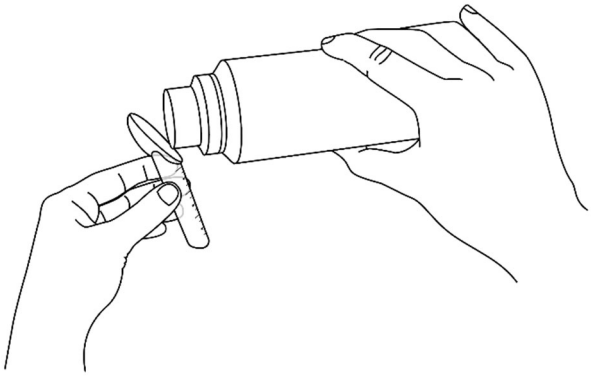
This leaflet was last revised in:

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

There are also links to other websites about rare diseases and treatments.



Package leaflet: Information for the patient

PHEBURANE 350 mg/mL oral solution
sodium phenylbutyrate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PHEBURANE is and what it is used for

PHEBURANE contains the active substance sodium phenylbutyrate which is used to treat patients with urea cycle disorders. These rare disorders are due to a deficiency of certain liver enzymes which are necessary to eliminate waste nitrogen in the form of ammonia.

Nitrogen is a building block of proteins, which are an essential part of the food we eat. As the body breaks down protein after eating, waste nitrogen, in the form of ammonia, accumulates because the body cannot eliminate it. Ammonia is especially toxic for the brain and leads, in severe cases, to reduced levels of consciousness and to coma.

PHEBURANE helps the body to eliminate waste nitrogen, reducing the amount of ammonia in your body. However PHEBURANE oral solution must be used along with a diet reduced in proteins, designed especially for you by the doctor and the dietician. You must follow this diet carefully.

2. What you need to know before you take PHEBURANE

Do not take PHEBURANE if you:
- are allergic to sodium phenylbutyrate or any of the other ingredients of this medicine (listed in section 6).
- are pregnant.
- are breast-feeding.

Warnings and precautions
Talk to your doctor or pharmacist before taking PHEBURANE if you:
- suffer from congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body) or a decrease in your kidney function.
- have decreased kidney or liver function, since PHEBURANE oral solution is eliminated from the body through the kidney and liver.

PHEBURANE will not prevent the occurrence of an acute excess of ammonia in the blood, a condition which usually constitutes a medical emergency. If this happens you will develop

symptoms such as feeling sick (nausea), being sick (vomiting), confusion and will need to get urgent medical help.

If you need laboratory tests, it is important to remind your doctor that you are taking PHEBURANE oral solution, since sodium phenylbutyrate may interfere with certain laboratory test results (such as blood electrolytes or protein, or liver function tests)

In case of any doubt, ask your doctor or pharmacist.

Other medicines and PHEBURANE
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is especially important to tell your doctor if you are taking medicines containing:
- valproate (an antiepileptic medicine).
- haloperidol (used in certain psychotic disorders).
- corticosteroids (medicines that are used to provide relief for inflamed areas of the body),
- probenecid (for treatment of hyperuricaemia, high levels of uric acid in the blood, associated with gout).

These medicines may change the effect of PHEBURANE and you will need more frequent blood tests. If you are uncertain if your medicines contain these substances, you should check with your doctor or pharmacist.

Pregnancy and breast-feeding
Do not use PHEBURANE if you are pregnant, because this medicine can harm your unborn baby.

If you are a woman who could get pregnant, **you must use reliable contraception, during treatment with PHEBURANE**. Talk to your doctor for the details.

Do not use PHEBURANE if you are breast-feeding, because this medicine can pass into the breast milk and may harm your baby.

Driving and using machines
PHEBURANE oral solution is unlikely to affect your ability to drive and use machines.

PHEBURANE oral solution contains sodium
This medicine contains 124 mg (5.4 mmol) sodium (main component of cooking/table salt) in each g dose of sodium phenylbutyrate. This is equivalent to 6.2% of the recommended maximum daily dietary intake of sodium for an adult.
The maximum daily dose of this medicine contains 2.5 g sodium This is equivalent to 125% of the recommended maximum daily dietary intake of sodium for an adult.
Talk to your doctor or pharmacist if you need 3 or more grams daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

PHEBURANE oral solution contains aspartame
This medicine contains 5.7 mg of aspartame per g dose of sodium phenylbutyrate. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Blackcurrant flavour topping contains propylene glycol
This medicine contains 26.55 mg of propylene glycol per drop.

If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

3. How to take PHEBURANE oral solution

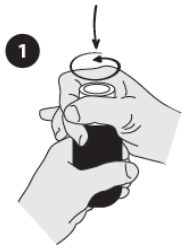
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dose
The daily dose of PHEBURANE oral solution will be based on your body weight or body surface and adjusted according to your protein tolerance and diet. You will need regular blood tests to determine the correct daily dose. Your doctor will tell you the amount of liquid you should take.

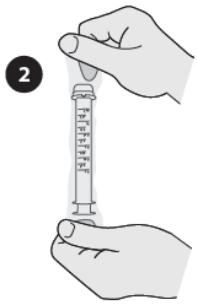
Method of administration
PHEBURANE oral solution should be taken with meals.
Use only the dosing syringe provided with PHEBURANE oral solution to measure a dose of PHEBURANE oral solution. Do not use other devices/spoons/syringes to administer a dose. The syringe is ranging from 0.5 g to 3 g with 0.25 increments. The graduation of the dosing syringe reflects the grams of sodium phenylbutyrate. Follow the instructions below to administer PHEBURANE oral solution:

Administration for oral use

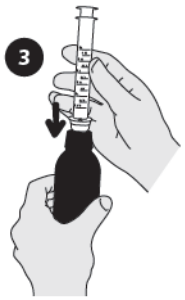
1. Open the bottle of PHEBURANE oral solution by pushing down on the cap and twisting to the left.



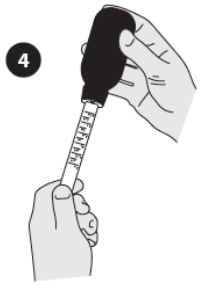
2. Take the CE marked dosing syringe with attached bottle adapter from the sachet.



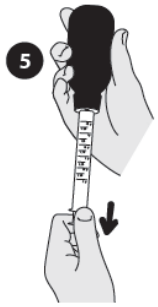
3. Place (push) the adapter in the neck of the bottle while the syringe is in the adapter.



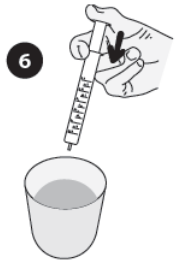
4. Invert the bottle.



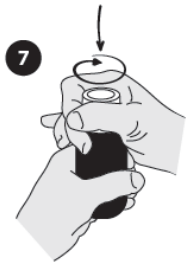
5. Take the required quantity of PHEBURANE oral solution from the bottle (equivalent to the number of grams sodium phenyl butyrate as prescribed by your doctor) with use of the dosing syringe.



6. Take the dosing syringe with PHEBURANE oral solution out of the adapter and pour the quantity of PHEBURANE oral solution in the dosing syringe into a glass with minimum 20 ml water.

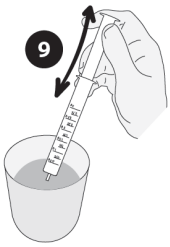


7. Close the bottle with PHEBURANE oral solution without removing the bottle adapter inserted in the neck of the bottle.



8. Add **one drop** of the flavour topping of your like (blackcurrant or lemon-mint) to the content of the glass of water; swirl gently, and then drink (If one drop of flavour topping would not provide the taste intensity of your like, you could use 2 drops).

9. After each administration, wash the syringe with cold to lukewarm water only.



PHEBURANE oral solution must be taken with a special diet reduced in protein.

You should take PHEBURANE oral solution with each meal or feeding. In small children this can be 4 to 6 times per day.

PHEBURANE oral solution can also be administered by nasogastric or gastrostomy tubes. PHEBURANE oral solution can be administered with tubes of a diameter of 2 mm (7-8 French) and larger. Use the provided oral syringe to measure your dose and follow the instructions below:

Preparation for nasogastric tube or gastrostomy tube administration

1. Follow Step 1 to Step 5 of the *Method of administration for oral use*;
2. The oral solution of Pheburane is ready-to use and no dilution is needed;
3. When used via nasogastric/gastrostomy **the flavour topping should not be added**;
4. Insert the tip of the syringe filled with the medicine onto the tip of the nasogastric/gastrostomy tube;
5. Use the plunger of the dosing syringe to administer the prescribed dose of PHEBURANE oral solution into the nasogastric/gastrostomy tube;
6. After each administration, the tube should be flushed once with the adequate volume of lukewarm water and allowed to drain. For adults, 20 ml of lukewarm water should be used. For children weighing less than 20 kg and neonates use 3 mL of water.

You will need to take this medicine and to follow a diet throughout your life.

If you take more PHEBURANE oral solution than you should
Patients who have taken very high doses of sodium phenylbutyrate experienced:
- sleepiness, tiredness, light-headedness and less frequently confusion;
- headache;
- changes in taste (taste disturbances);
- decrease in hearing;
- disorientation;
- impaired memory;
- worsening of existing neurological conditions.

If you experience any of these symptoms, you should immediately contact your doctor or the nearest hospital emergency department for supportive treatment.

If you forget to take PHEBURANE oral solution
You should take a dose as soon as possible with your next meal. Make sure that there are at least 3 hours between two doses. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If persistent vomiting occurs, you should contact your doctor immediately.

Very common side effects (may affect more than 1 in 10 people)
irregular menstrual periods and stopping of menstrual periods in fertile women.
If you are sexually active and your period stops altogether, do not assume that this is caused by PHEBURANE oral solution. If this occurs, please discuss it with your doctor, because the absence of your period may be caused by pregnancy (see 'Pregnancy and breast-feeding' section above) or by menopause.

Common side effects (may affect more than 1 in 100 people)
changes in number of blood cells (red cells, white cells and platelets), changes in the amount of bicarbonate in the blood, reduced appetite, depression, irritability, headache, fainting, fluid retention (swelling), changes in taste (taste disturbances), stomach ache, vomiting, nausea, constipation, abnormal skin door, rash, abnormal kidney function, weight gain, altered laboratory test values.

Uncommon side effects (may affect more than 1 in 1,000 people)
deficiency in red blood cells due to failure of the bone marrow, bruising, altered heart rhythm, rectal bleeding, inflammation of the stomach, stomach ulcer, inflammation of the pancreas.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store PHEBURANE oral solution

Keep this medicine out of the sight and reach of children.

Do not use PHEBURANE oral solution after the expiry date which is stated on the carton and the bottle label after EXP. The expiry date refers to the last day of that month.

Once the PHEBURANE oral solution bottle is first open, you must use your medicine within 4 weeks of opening. The bottle should be discarded even if it is not empty.

Once the flavour bottle is first open, you must use it within 4 weeks of opening. The bottle should be discarded even if it is not empty.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PHEBURANE oral solution contains
- The active substance is sodium phenylbutyrate. Each mL of liquid contains 350 mg of sodium phenylbutyrate.

- The other ingredients are: purified water, aspartame (E951), sucralose (E955), glycerol (E422), hydroxyethylcellulose (E1525) (See section 2 “PHEBURANE oral solution contains aspartame”).

Flavour toppings:
- Blackcurrant flavour topping consisting of blackcurrant and mint flavouring, containing propylene glycol (E1520).
- Lemon-mint flavour topping consisting of lemon and mint flavouring.

What PHEBURANE oral solution looks like and contents of the pack
PHEBURANE oral solution is clear, colourless to pale yellow liquid.

Each pack contains:
- One amber glass bottle containing 100 mL of the oral solution and closed with a plastic child-resistant cap;
- One dosing syringe with ranging from 0.5 g to 3 g with 0.25 increments to measure the dose in grams of sodium phenylbutyrate;
- Bottle Adapter,
- One amber glass bottle containing 3 mL of lemon-mint flavour topping,
- One amber glass bottle containing 3 mL of blackcurrant flavour topping.

Marketing Authorisation Holder and Manufacturer
Eurocept International BV
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1244 RL Ankeveen
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

There are also links to other websites about rare diseases and treatments.