

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/m²/day in children weighing more than 20 kg, adolescents and adults.

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

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/m²/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/m²/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.

A calibrated dosing spoon is provided which 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, 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 low salt diet.
- This medicinal product contains 768 mg sucrose per gram. 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to

<1/100), rare ($\geq 1/10,000$ 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
<i>Blood and lymphatic system disorders</i>	Common	anaemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
	Uncommon	aplastic anaemia, ecchymosis
<i>Metabolism and nutrition disorders</i>	Common	metabolic acidosis, alkalosis, decreased appetite
<i>Psychiatric disorders</i>	Common	depression, irritability
<i>Nervous system disorders</i>	Common	syncope, headache
<i>Cardiac disorders</i>	Common	oedema
	Uncommon	arrhythmia
<i>Gastrointestinal disorders</i>	Common	abdominal pain, vomiting, nausea, constipation, dysgeusia
	Uncommon	pancreatitis, peptic ulcer, rectal haemorrhage, gastritis
<i>Skin and subcutaneous tissue disorders</i>	Common	rash, abnormal skin odor
<i>Renal and urinary disorders</i>	Common	renal tubular acidosis
<i>Reproductive system and breast disorders</i>	Very common	amenorrhea, irregular menstruation
<i>Investigations</i>	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, pancytopenia, 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 orthotopic 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 (sucrose and maize starch),
hypromellose,
ethylcellulose N7,
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

Lucane Pharma

172 rue de Charonne
75011 Paris
France

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:

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(S) 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

Lucane Pharma
172 rue de Charonne
75011 Paris
France

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**

The requirements for submission of periodic safety update reports 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)**

Not applicable.

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

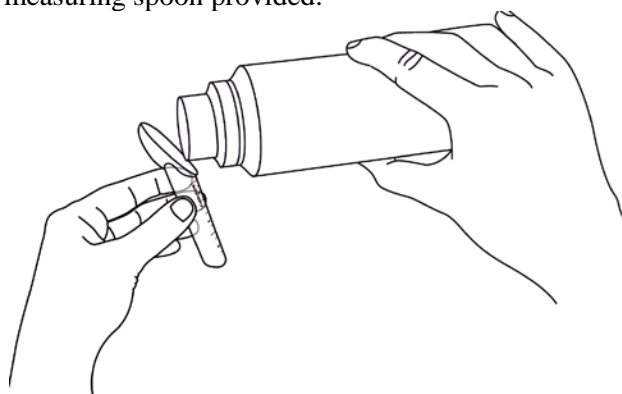
Contains sodium and sucrose.
See package leaflet for further information.

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

Lucane Pharma
172 rue de Charonne
75011 Paris - France

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:

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
2. What you need to know before you take PHEBURANE
3. How to take PHEBURANE
4. Possible side effects
5. How to store PHEBURANE
6. Contents of the pack and other information

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.

PHEBURANE 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) of sodium per 1 g of sodium phenylbutyrate. 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 of sucrose per 1 g of sodium phenylbutyrate. 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.

Dosage

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.

A calibrating measuring spoon which dispenses up to 3 g of sodium phenylbutyrate is provided with the medicine. Only use this measuring spoon to measure out the dose.

To measure the dose:

- Lines on the spoon indicate the amount (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 at the end of/page 2 of 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 odor, 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 desiccant.

Each bottle contains 174g of granules.

Each carton contains 1 bottle.

A calibrating measuring spoon is provided.

Marketing Authorisation Holder and Manufacturer

Lucane Pharma
172 rue de Charonne
75011 Paris - France

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

België/Belgique/Belgien

Lucane Pharma
Tél/Tel: + 33 153 868 750
info@lucanepharma.com

България

Lucane Pharma
Тел.: + 33 153 868 750
info@lucanepharma.com

Česká republika

Medical Need Europe AB
Tel: + 46 8 533 39 500
info@medicalneed.com

Danmark

Medical Need Europe AB
Tlf: + 46 8 533 39 500
info@medicalneed.com

Deutschland

Lucane Pharma
Tel: + 33 153 868 750
info@lucanepharma.com

Eesti

Medical Need Europe AB
Tel: + 46 8 533 39 500
info@medicalneed.com

Ελλάδα

Lucane Pharma
Τηλ: + 33 153 868 750
info@lucanepharma.com

España

Lucane Pharma
Tel: + 33 153 868 750
info@lucanepharma.com

France

Lucane Pharma
Tél: + 33 153 868 750
info@lucanepharma.com

Lietuva

Medical Need Europe AB
Tel: + 46 8 533 39 500
info@medicalneed.com

Luxembourg/Luxemburg

Lucane Pharma
Tél/Tel: + 33 153 868 750
info@lucanepharma.com

Magyarország

Medical Need Europe AB
Tel.: + 46 8 533 39 500
info@medicalneed.com

Malta

Lucane Pharma
Tel: + 33 153 868 750
info@lucanepharma.com

Nederland

Lucane Pharma
Tel: + 33 153 868 750
info@lucanepharma.com

Norge

Medical Need Europe AB
Tlf: + 46 8 533 39 500
info@medicalneed.com

Österreich

Lucane Pharma
Tel: + 33 153 868 750
info@lucanepharma.com

Polska

Medical Need Europe AB
Tel.: + 46 8 533 39 500
info@medicalneed.com

Portugal

Lucane Pharma
Tel: + 33 153 868 750
info@lucanepharma.com

Hrvatska

Lucane Pharma

Tel: + 33 153 868 750

info@lucanepharma.com**Ireland**

Lucane Pharma

Tel: + 33 153 868 750

info@lucanepharma.com**Ísland**

Medical Need Europe AB

Sími: + 46 8 533 39 500

info@medicalneed.com**Italia**

Lucane Pharma

Tel: + 33 153 868 750

info@lucanepharma.com**Κύπρος**

Lucane Pharma

Τηλ: + 33 153 868 750

info@lucanepharma.com**Latvija**

Medical Need Europe AB

Tel: + 46 8 533 39 500

info@medicalneed.com**România**

Lucane Pharma

Tel: + 33 153 868 750

info@lucanepharma.com**Slovenija**

Medical Need Europe AB

Tel: + 46 8 533 39 500

info@medicalneed.com**Slovenská republika**

Medical Need Europe AB

Tel: + 46 8 533 39 500

info@medicalneed.com**Suomi/Finland**

Medical Need Europe AB

Puh/Tel: + 46 8 533 39 500

info@medicalneed.com**Sverige**

Medical Need Europe AB

Tel: + 46 8 533 39 500

info@medicalneed.com**United Kingdom**

Lucane Pharma

Tel: + 33 153 868 750

info@lucanepharma.com**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.

