Date: 16 September 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Pheburane

International non-proprietary name: natrii phenylbutyras
Pharmaceutical form: Granules
Dosage strength: 483 mg/g
Route(s) of administration: oral
Marketing Authorisation Holder: NordMedica SA
Marketing Authorisation No.: 67263
Decision and Decision date: approved on 29 July 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance, sodium phenylbutyrate, of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 29 January 2019.

Authorisation in accordance with Art. 14 para. 1 a^{bis} TPA
The applicant requested a simplified authorisation in accordance with Art. 14 para. 1 a^{bis} TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

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

2.2.2 Approved Indication

PHEBURANE is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.
It is indicated in all patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

2.2.3 Requested Dosage

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 newborns, infants and children weighing less than 20 kg
- 9.9 - 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults.

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

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	18 February 2019
Formal control completed	29 May 2019
List of Questions (LoQ)	13 September 2019
Answers to LoQ	15 January 2020
Predecision	8 April 2020
Answers to Predecision	4 September 2020
Final Decision	29 July 2020
Decision	approval

For the application for the authorisation of the medicinal product Pheburane granules, Swissmedic has reviewed the quality exclusively on the basis of primary data. The authorisation of Pheburane granules is based primarily on the medicinal product Ammonaps granules, 940 mg/g, which contains the same active substance and has been authorised in the EU for more than 10 years. Apart from the quality-related aspects for which Swissmedic has conducted an independent scientific review, this SwissPAR refers to the authorisation of the foreign medicinal product Ammonaps granules, 940 mg/g.

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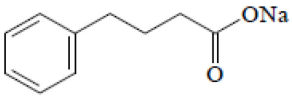
3 Quality Aspects

3.1 Drug Substance

INN: Sodium phenylbutyrate
Chemical name: 4-Phenylbutyric acid sodium salt
Molecular formula: $C_{10}H_{11}NaO_2$
Molecular mass: 186.2 g/mol
Molecular structure: non-chiral



Physico-chemical properties: Sodium phenylbutyrate is a white or yellowish-white hygroscopic powder, which is freely soluble in water and ethanol and practically insoluble in methylene chloride.

Synthesis: Sodium phenylbutyrate is manufactured in a two-step, or alternatively in a three-step, process using well-defined starting materials and reagents.

Specification: To ensure a consistent quality of sodium phenylbutyrate, the specifications include tests for appearance, solubility, identity (IR, test for sodium), pH, assay (titration), impurities (HPLC, GC), residual solvents (GC), water content (KF) and heavy metals, according to Ph. Eur. monograph no. 04/2008:2183. Residual solvents used in the final stage of synthesis (methanol and acetone) are controlled by an additional, adequately validated method, in accordance with the ICH guideline of residual solvents (ICH Q3C).

Stability: Due to hygroscopicity, the bulk drug substance is stored in containers, suitable to protect from moisture. Based on stability studies, carried out according to the current guideline recommendations, a satisfactory retest period was established.

3.2 Drug Product

Description and composition: The drug product is presented as granules containing 483 mg/g sodium phenylbutyrate. The excipients are sugar spheres (core of granules), hypromellose (film-coating agent), ethylcellulose (film-coating agent), macrogol (plasticiser) and povidone (binder).

Pharmaceutical development: Sodium phenylbutyrate has a very unpleasant taste, resulting in serious difficulties in compliance with treatment, especially for children. Pheburane granules are therefore coated to mask the unpleasant bitter taste of the active substance.

Manufacture: The manufacturing process is described with a sufficient level of detail in order to achieve consistent granule quality. Appropriate in-process controls are applied.

Specification: The finished product release specifications include appropriate tests for appearance, identification (HPLC, IR), dissolution, water content (KF), tapped density, integrity of coating (in-house method), residual ethanol (GC), uniformity of mass of delivered dose, assay and related substances (HPLC) and microbiological purity. The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container-Closure System: HDPE bottles with child-proof caps and desiccant contain 174 g of granules (which corresponds to 84 g of sodium phenylbutyrate). Each bottle is packed in an outer carton and is accompanied by a calibrated dosing spoon (graduation of 250 mg) that dispenses up to 3 g of sodium phenylbutyrate.

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Stability: Appropriate stability data, including in-use stability, are presented for industrial-scale batches. Based on these data, a shelf-life was established for the Pheburane granules. The storage recommendation is “Do not store above 25°C”.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

In accordance with Art. 14 para. 1 a$^{bis-quater}$ TPA, Swissmedic has not reviewed any nonclinical data for the authorisation of the medicinal product Pheburane, granules. The authorisation of Pheburane granules is based on the medicinal product Ammonaps granules, 940 mg/g, which contains the same active substance and has been authorised in the EU for more than 10 years. This SwissPAR refers to the authorisation of the foreign comparator medicinal product Ammonaps granules, 940 mg/g.

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5 Clinical and Clinical Pharmacology Aspects

For the application for the authorisation of the medicinal product Pheburane, granules, Swissmedic has conducted only a summary review of the efficacy and safety.
The authorisation of Pheburane granules is based primarily on the medicinal product Ammonaps granules, which contains the same active substance and has been authorised in the EU for more than 10 years. This SwissPAR refers to the authorisation of the foreign comparator product Ammonaps granules.
Since differences exist between the two products in respect of pharmaceutical form and excipient composition, a bioequivalence study (# 109551) was submitted. This study can be used for the bridging between the proposed product Pheburane, granules, and the reference product Ammonaps, granules, since bioequivalence, based on C_{max} and AUC, was demonstrated.

5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Pheburane, granules was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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PHEBURANE 483 mg/g granules

The effectiveness and safety of PHEBURANE have only been reviewed by Swissmedic at a summary level. The approval of PHEBURANE is based on AMMONAPS with date of revision July 2019, which contains the same active ingredient and is approved in the EU.

Composition

Active substances

Sodium phenylbutyrate

Excipients

Sugar spheres (corresp. to sucrose and maize starch), hypromellose, ethylcellulose, macrogol 1500, povidone K25.
One gram of granules contains 59.8 mg of sodium and 371 mg of sucrose, equivalent to 124 mg of sodium and 768 mg of sucrose per gram of sodium phenylbutyrate.

Pharmaceutical form and active substance quantity per unit

White to off-white granules.
Each gram of granules contains 483 mg of sodium phenylbutyrate

Indications/Uses

PHEBURANTE is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.
It is indicated in all patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

Dosage/Administration

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

Dose adjustment/titration

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.

Usual dosage

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 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.

Special dosage instructions

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.

Children and adolescents

Dosage instructions for children and adolescents see chapter "usual dosage".

Mode 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.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy.
- Breast-feeding.

Warnings and precautions

PHEBURANE is considered high in sodium. This should be taken into account especially in patients on a low sodium diet. 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.
This medicinal product contains 124 mg (5,4 mmol) of sodium per gram of sodium phenylbutyrate, equivalent to 6.2 % of the WHO recommended maximum daily intake for sodium for adults.
The maximum daily dose of this medicinal product (2.5 g (108 mmol) of sodium per 20 g of sodium phenylbutyrate) is equivalent to 125 % of the WHO recommended maximum daily intake for sodium.
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.
Serum potassium should be monitored during therapy since renal excretion of phenylacetylglutamine may induce a urinary loss of potassium.
PHEBURANTE contains sucrose. 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.
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.

Interactions

Pharmacokinetic interactions

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.

Pregnancy, lactation

Pregnancy

Effective contraceptive measures must be taken by women of child-bearing potential.

There are no sufficient data on the use of sodium phenylbutyrate in pregnant women. Studies in animals have shown reproductive toxicity (see section “Preclinial Data”). The importance of these results for pregnant women is unknown; Pheburane is therefore contra-indicated in pregnancy.

Lactation

It is unknown whether Phenylacetate is excreted in human milk, and therefore PHEBURANE is contra-indicated during breast-feeding (see section “Preclinical Data”).

Fertility

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

Effects on ability to drive and use machines

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

Undesirable effects

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.
The frequency should be stated as follows:
"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1000, <1/100)
"rare" (≥1/10,000, <1/1000)
"very rare" (<1/10,000)

Reproductive system and breast disorders
Very common: amenorrhea, irregular menstruation
Skin and subcutaneous tissue disorders
Common: rash, abnormal skin odor
Renal and urinary disorders
Common: renal tubular acidosis
Blood and lymphatic system disorders
Common: anaemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis
Uncommon: aplastic anaemia, ecchymosis
Gastrointestinal disorders
Common: abdominal pain, vomiting, nausea, constipation, dysgeusia
Uncommon: pancreatitis, peptic ulcer, rectal haemorrhage, gastritis
Nervous system disorders
Common: syncope, headache

Cardiac disorders

Common: oedema

Uncommon: arrhythmia

Psychiatric disorders

Common: depression, irritability

Metabolism and nutrition disorders

Common: metabolic acidosis, alkalosis, decreased appetite

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 undesirable effects

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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Signs and symptoms

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.

Treatment

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

Properties/Effects

ATC code

A16AX03

Mechanism of action

Pharmacodynamics

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

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.

Safety and efficacy in paediatric patients

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.

Pharmacokinetics

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.

Metabolism

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.

Elimination

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

Preclinical data

Mutagenicity

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

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

Reproductive toxicity

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 “Pregnancy, lactation”).

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 “Pregnancy, lactation”).

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Shelf life after opening: 45 days

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.
Instructions for handling

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

Authorisation number

67263 (Swissmedic)

Packs

Pheburane 483 mg/g in HDPE bottle, child-resistant closure with desiccant, containing 174 g of granules.
Each carton contains one bottle.
A calibrated measuring spoon is provided.

Marketing authorisation holder

Nordmedica SA, Agno

Date of revision of the text

Comparative foreign medicinal product: July 2019
Without security-relevant additions from Swissmedic: April 2020

Revision history

Datum	Versions Nr.	Milestone	Status	Bemerkung/Änderung
06.02.2019	V001	MA application	Draft	New SmPC
12.12.2019	V001	Rt List of Questions	Draft	
04.05.2020	V001	Rt Preapproval	Draft	
29.07.2020	V001	Approval MA	approved	