French National Agency for Medicines and Health Products Safety

CERTIFICATE NUMBER: ***2018/HPF/FR/032***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1, 2]

Part 1

Issued following an inspection in accordance with :
Art. 111(5) of Directive 2001/83/EC as amended

The competent authority of France confirms the following:
The manufacturer: ***LUCANE PHARMA - PARIS***
Site address: ***172 rue de Charonne, PARIS, 75011, France***

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. ***MM 18/038*** in accordance with Art. 40 of Directive 2001/83/EC transposed in the following national legislation:
Art. L.5124-3 of Public Health Code

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2017-11-09*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC [3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

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[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*

[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products

1 MANUFACTURING OPERATIONS	
1.1	**Sterile products**
	1.1.3 Batch certification
1.2	**Non-sterile products**
	1.2.2 Batch certification
1.5	**Packaging**
	1.5.2 Secondary packing

2 IMPORTATION OF MEDICINAL PRODUCTS	
2.2	**Batch certification of imported medicinal products**
	2.2.1 Sterile products 2.2.1.1 Aseptically prepared 2.2.1.2 Terminally sterilised
	2.2.2 Non-sterile products
2.3	**Other importation activities**
	2.3.1 Site of physical importation
	2.3.2 Importation of intermediate which undergoes further processing

Clarifying remarks (for public users)

There are no quality control facilities. Importation activity is limited to batch certification, sampling, taking and holding of reference samples of packaging material and finished product. --- Signatory: Mrs Mélanie Cachet, head of pharmaceutical product inspection and counterfeiting fight department. - The ANSM does not issue paper copies of good practice certificates.

2018-02-23

Name and signature of the authorised person of the Competent Authority of France

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French National Agency for Medicines and Health Products Safety
Tel: ***Confidential***
Fax: ***Confidential***

Agencia Nacional Francesa para la Seguridad de los Medicamentos y los Productos para la Salud

CERTIFICADO NÚMERO: *2018/HFP/FR/032*

CERTIFICADO DE CUMPLIMIENTO DE LAS BPM DE UN FABRICANTE [1,2]

Parte 1

Emitido siguiendo una inspección de acuerdo con:
Art. 111(5) de la Directriz 2001/83/EC según su modificación

La autoridad competente de Francia confirma lo siguiente:
El fabricante: **LUCANE PHARMA – PARIS**
Dirección de la planta: **172 rue de Charonne, PARIS, 75011, Francia**

Ha sido inspeccionado bajo el programa de inspección nacional en conexión con la autorización de manufactura No. **MM 18/038**, de acuerdo con el Art. 40 de la Directriz 2001/83/EC transpuesto en la siguiente legislación nacional:
Art. L.5124-3 del Código de Salud Pública

Según el conocimiento adquirido durante la inspección del fabricante, la última de las cuales fue realizada en **2017-11-09**, se considera que cumple con:

- Los principios y guías de la Buenas Prácticas de Manufactura establecidas en la Directriz 2003/94/EC [3]

Este certificado refleja la condición de la planta de manufactura al momento de la inspección mencionado atrás y no se debe considerar que refleja la condición de cumplimiento si han transcurrido más de tres años desde la fecha de la inspección. Sin embargo, este período de validez puede ser reducido o extendido usando los principios regulatorios de gestión de riesgos, mediante una anotación en el espacio correspondiente a Restricciones u Observaciones Aclaratorias. Este certificado es

válido solamente cuando se presenta con todas las páginas de las Partes 1 y 2. La autenticidad de este certificado puede ser verificada en EudraGMDP. Si no aparece, favor contactar a la autoridad que lo ha emitido.

Parte 2

Medicamentos humanos

1 OPERACIONES DE MANUFACTURA	
1.1	**Productos estériles**
	1.1.3 Certificación de lotes
1.2	**Productos no estériles**
	1.2.2 Certificación de lotes
1.5	**Empaque**
	1.5.2 Empaque secundario

2 IMPORTACIÓN DE MEDICAMENTOS	
2.2	**Certificación de lotes de medicamentos importados**
	2.2.1 Productos estériles 2.2.1.1 Asépticamente preparados 2.2.1.2 Estériles como productos terminados
	2.2.2 Productos no estériles
2.3	**Otras actividades de importación**
	2.3.1 Sitio de la importación física
	2.3.2 Importación de productos intermedios sometidos a procesos posteriores

[1] El certificado referido en los parágrafos 111(5) de la Directriz 2001/83/EC y 80(5) de la Directriz 2001/82/EC debe ser requerido para las importaciones procedentes de terceros países con destino a un Estado Miembro.

[2] Las guías para la interpretación de este formato se pueden encontrar en el menú de ayuda de la base de datos de EudraGMDP.

[3] Estos requerimientos cumplen con las recomendaciones de BPM de la OMS.

Luz Helena Velásquez
TRADUCTORA OFICIAL
OFFICIAL TRANSLATOR
Resolución No. 1704 de 1991
Minjusticia

Observaciones aclaratorias (para usuarios públicos)

No hay instalaciones de control de calidad. La actividad de importación está limitada a la certificación de lotes, muestreo, toma y retención de muestras de referencia del material de empaque y producto terminado. ---- Firmante: Mrs Mélanie Cachet, directora del departamento de inspección de productos farmacéuticos y lucha contra la falsificación. ---- ANSM no emite copias impresas de certificados de buenas prácticas.

2018-02-23 Nombre y firma de la persona autorizada de la Autoridad Competente de Francia

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Agencia Nacional Francesa para la Seguridad de los Medicamentos y los Productos para la Salud
Tel: Confidencial
Fax: Confidencial

Luz Helena Velásquez
TRADUCTORA OFICIAL
OFFICIAL TRANSLATOR
Resolución No. 1704 de 1991
Minjusticia

EUROPEAN MEDICINES AGENCY

Certificate: 01/20/142129
Request: 77487

Certificate of a Medicinal Product[1]
Certificado de Medicamento[1]
Certificat de Médicament[1]

This Certificate conforms to the format recommended by the World Health Organization. (Explanatory notes attached) /
El presente certificado se adapta al formato recomendado por la Organización Mundial de la Salud. (Se adjuntan notas explicativas) /
Ce Certificat est conforme à la présentation recommandée par l'Organisation Mondiale de la Santé. (Voir notes explicatives ci-jointes)

No. of Certificate / N° de certificado / N° du certificat: ***01/20/142129***

Exporting (Certifying) region / Región exportadora (que certifica) / Région d'exportation (certificateur) :
European Union / Unión Europea / Union Européenne :

Belgium, Bulgaria, Czechia, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, Sweden and United Kingdom.

Bélgica, Bulgaria, Chequia, Dinamarca, Alemania, Estonia, Irlanda, Grecia, España, Francia, Croatie, Italia, Chipre, Letonia, Lituania, Luxemburgo, Hungría, Malta, Paises Bajos, Austria, Polonia, Portugal, Rumanía, Eslovenia, Eslovaquia, Finlandia, Suecia y Reino Unido.

Belgique, Bulgarie, Tchéquie, Danemark, Allemagne, Estonie, Irlande, Grèce, Espagne, France, Croacia, Italie, Chypre, Lettonie, Lituanie, Luxembourg, Hongrie, Malte, Pays-Bas, Autriche, Pologne, Portugal, Roumanie, Slovénie, Slovaquie, Finlande, Suède et Royaume-Uni.

As of 1.2.2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period /
Depuis le 1er février 2020, le Royaume-Uni n'est plus un État membre de l'UE . Cependant, il continue d'être soumis au droit de l'UE pendant la période transitoire /
A partir del 1 de febrero de 2020, el Reino Unido dejará de ser Estado miembro de la UE. Sin embargo, el Derecho de la UE se seguirá aplicando en el Reino Unido durante el período de transición

Importing (requesting) country / País importador (solicitante) / Pays importateur (sollicitant):

COLOMBIA

1 Name and pharmaceutical form of the product / Nombre y forma farmaceútica del medicamento / Dénomination et forme pharmaceutique du médicament:

PHEBURANE Granules

1.1 Active substance(s)[2] and amount(s) per unit dose or unit volume[3]:
Principio(s) activo(s)[2] y cantidad(es) por unidad de dosis o unidad de volumen[3]:
Substance(s) active(s)[2] et quantité(s) par unité de dose ou unité de volume[3]:

Sodium phenylbutyrate; 483 mg/g; 1 bottle + 1 dosing spoon

For complete composition including excipients, see attached. [4]/ Para la composición completa incluidos los excipientes, véase información anexa. [4] / La composition complète du médicament, y compris les excipients, voir annexe. [4]

1.2 Is this product subject to a Community Marketing Authorisation? [5]
¿Está sujeto este medicamento a una autorización de comercialización comunitaria? [5]
Ce médicament fait-il l'objet d'une autorisation communautaire de mise sur le marché ? [5]

yes

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1.3 Is this product actually on the market in the exporting region?
¿Se encuentra este medicamento en el mercado de la región exportadora?
Ce médicament est- il actuellement commercialisé dans la région exportatrice?

yes

2.1 Number in the Community Register of Medicinal Products [7] and date of issue:
Número de autorización de comercialización comunitaria [7] y fecha de emisión:
Numéro au registre communautaire de mise sur le marché [7] et date de délivrance:

EU/1/13/822/001, 31.7.2013

2.2 Community Marketing Authorisation Holder (name and address):
Titular de la autorización de comercialización comunitaria (nombre y dirección):
Titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) :

Eurocept International BV, Trapgans 5, 1244 RL Ankeveen, The Netherlands.

2.3 Status of the Community Marketing Authorisation Holder: [8]
Estatus del titular de la autorización de comercialización comunitaria: [8]
Statut du titulaire de l'autorisation communautaire de mise sur le marché : [8]

c

2.3.1 For categories (b) and (c) the name and address of the manufacturer producing the pharmaceutical form is: [9]
Para las categorías (b) y (c), el nombre y dirección del fabricante que produce la forma farmaceútica es: [9]
Pour les catégories (b) et (c), nom et l'adresse du fabricant de la forme pharmaceutique considérée : [9]

Rottendorf Pharma GmbH, Ostenfelder Strasse 51 – 61, 59320 Ennigerloh, Germany (also responsible for quality control). Sites responsible for batch release in the EU: Lucane Pharma, 172 rue de Charonne, 75011 Paris, France (site also responsible for secondary packaging) [AND] Eurocept International B.V., Trapgans 5, 1244 RL Ankeveen, The Netherlands. Site responsible for primary and secondary packaging: Rottendorf Pharma GmbH, Am Fleigendahl 3, 59320 Ennigerloh, Germany. Site responsible for secondary packaging: Tjoapack Netherlands BV, Nieuwe Donk 9, NL-4879 AC Etten-Leur, The Netherlands.

2.4 Is the European Public Assessment Report (EPAR) appended? [10]
¿Se adjunta el informe europeo público de evaluación (EPAR)? [10]
Un rapport européen public d'evaluation (EPAR) est-il annexé ? [10]

no

2.5 Is the attached, officially approved product information included in the Community Marketing Authorisation?[11]
¿Se incluye la información sobre el medicamento adjunto en la autorización de comercialización comunitaria?[11]
L'information sur le médicament, officiellement approuvée, fait elle partie de l'autorisation communautaire de mise sur le marché ? [11]

yes

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2.6 Applicant for the Certificate, if different from the Community Marketing Authorisation Holder (name and address): [12]
Solicitante del Certificado, si es diferente del titular de la autorización de comercialización comunitaria (nombre y dirección): [12]
Demandeur du Certificat, s'il est autre que le titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) : [12]

3. Does the Certifying Authority arrange for periodic inspections of the manufacturing site in which the pharmaceutical form is produced?
¿La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmaceútica?
L'autorité certificatrice organise-t-elle des inspections périodiques de l'usine de production de la forme pharmaceutique?

yes

If no or not applicable, proceed to question 4 / Si no o no aplicable, pase a la pregunta 4 / Si la réponse est non ou sans objet, passer à la question 4.

3.1 Periodicity of routine inspections: ***Frequency of inspections is determined on risk-based approach.***
Periodicidad de las inspecciones de rutina: ***La frecuencia de las inspecciones esta basada en función del riesgo.***
Périodicité des inspections de routine: ***L'évaluation du risque détermine la fréquence des inspections.***

3.2 Has the manufacture of this type of pharmaceutical form been inspected?
¿Se ha inspeccionado la fabricación de este tipo de forma farmaceútica?
La fabrication de ce type de forme pharmaceutique a-t-elle fait l'objet d'une inspection?

yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization? [15]
¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud? [15]
Est-ce que l'établissement pharmaceutique est conforme aux BPF recommandées par l'Organisation Mondiale de la Santé ? [15]

yes

4. Does the information submitted by the applicant satisfy the Certifying Authority on all aspects of the manufacture of the product undertaken by another party? [16]
¿La información presentada por el solicitante satisface a la autoridad de certificación en relación a todos los aspectos de la fabricación del medicamento realizada por terceros? [16]
Les informations fournies par le demandeur satisfont-elles aux exigences des autorités certificatrices sur tous les aspects de la fabrication du médicament pris en charge par une tierce partie ? [16]

yes

EUROPEAN MEDICINES AGENCY

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EUROPEAN MEDICINES AGENCY

Certificate: 01/20/142129
Request: 77487

Address of the Certifying Authority / Dirección de la autoridad certificadora / Adresse de l'autorité certificatrice :

European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

Telephone / Teléfono / Téléphone: ***+31 (0)88 781 6000***
E-mail / Correo electrónico / Courrier électronique: ***certificate@ema.europa.eu***

Name of authorised person / Nombre de la persona autorizada / Nom de la personne autorisée:

Verena Janiak

Signature / Firma / Signature:

Stamp and date / Sello y fecha / Tampon et date:

7.2.2020

EUROPEAN MEDICINES AGENCY

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Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the medicinal product and of the applicant for the Certificate in the exporting region at the time of issue. It is for a single product at a given point in time since manufacturing arrangements and approved information for different pharmaceutical forms and different strengths can vary.

[2] Whenever possible, International Non-proprietary Names (INNs) or national non-proprietary names are used.

[3] The formula (complete composition) of the pharmaceutical form is appended.

[4] Provision of the details of quantitative composition is attached on request of the Community Marketing Authorisation Holder.

[5] When applicable, details are appended of any conditions or restrictions applied to the supply and use of the product that is entered into the Community Marketing Authorisation.

[6] Not applicable.

[7] Indicated, when applicable, if the Community Marketing Authorisation has been granted under exceptional circumstances, conditional approval or if the product has not yet been approved.

[8] The person responsible for placing the product on the market:

(a) manufactures the pharmaceutical form;
(b) packages and/or labels a pharmaceutical form manufactured by an independent company; or
(c) is involved in none of the above.

[9] This information can only be provided with the consent of the Community Marketing Authorisation Holder or, in the case of non-registered products, the applicant. Non-completion of this section (2.3.1) indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the Community Marketing Authorisation. If the production site is changed, the Community Marketing Authorisation has to be updated or it is no longer valid.

[10] This refers to the document that summarises the technical basis on which the product has been authorised.

[11] This refers to the product information which forms a part of the Community Marketing Authorisation, such as the Summary of Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the Community Marketing Authorisation Holder. This permission has to be provided to the European Medicines Agency by the applicant.

[13] If applicable the reason why the medicinal product does not have a Community Marketing Authorisation, e.g.:

(a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases - not endemic in the exporting region;
(b) the product has been reformulated with a view to improving its stability under tropical conditions;
(c) the product has been reformulated to exclude excipients not approved for use in medicinal products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active substance;
(e) any other reason, as specified.

[14] "Not applicable" means the manufacture is taking place in a region other than that issuing the Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of medicinal products referred to in the Certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No 822, 1992, Annex 1).

[16] This section is to be completed when the Community Marketing Authorisation Holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the Certifying Authority with information to identify the contracting parties responsible for each stage of manufacture of the pharmaceutical form, and the extent and nature of any controls exercised over each of these parties.

STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

1. Name and pharmaceutical form of the Medicinal Product:
Nombre y forma farmacéutica del medicamento:
Dénomination et forme pharmaceutique du médicament:

Pheburane granules

2. Number(s) in the Community Register of Medicinal Products:
Número(s) de autorización de comercialización comunitaria:
Numéro(s) au registre communautaire de mise sur le marché:

EU/1/13/822/001

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento:
Composition qualitative et quantitative du médicament:

Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units: Cantidades y unidades: Quantités et unités:		
	Quantity per g of granules	Quantity per bottle of 174 g)	Function
Sodium 4-phenylbutyrate	483 mg	84 g	Drug substance
Other ingredient(s): Otros ingrediente(s): Excipient(s):	Quantities and units: Cantidades y unidades: Quantités et unités:		
Sugar spheres 250-355	403 mg	70.1 g	Neutral core
Hypromellose	40 mg	7.0 g	Film coating agent
Purified water*	-	-	Solvent
Ethylcellulose N7	58 mg	10.1 g	Film coating agent (Taste masking agent)
Macrogol 1500	6 mg	1.0 g	Plasticizer
Povidone K25	10 mg	1.8 g	Binder
Ethanol 96%*	-	-	Solvent

*evaporated during process

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 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.

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 (≥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/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

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: 23 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.