ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RAVICTI 1.1 g/ml oral liquid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of liquid contains 1.1 g of glycerol phenylbutyrate. This corresponds to a density of 1.1 g/ml.

3. PHARMACEUTICAL FORM

Oral liquid.
Clear, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RAVICTI is indicated for use as adjunctive therapy for chronic management of patients with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate synthetase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.
RAVICTI must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).

4.2 Posology and method of administration

RAVICTI should be prescribed by a physician experienced in the management of UCDs.

Posology

RAVICTI must be used with dietary protein restriction and sometimes dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements) depending on the daily dietary protein intake needed to promote growth and development.

The daily dose should be individually adjusted according to the patient's protein tolerance and the daily dietary protein intake needed.

RAVICTI therapy may be required life long unless orthotopic liver transplantation is elected.

Adults and children
The recommended dose for patients naïve to phenylbutyric acid and for patients switching from sodium phenylbutyrate or from sodium phenylacetate/sodium benzoate injection to RAVICTI are different.

The recommended total daily dose of RAVICTI is based on body surface area and ranges from 4.5 ml/m^2/day to 11.2 ml/m^2/day (5.3 g/m^2/day to 12.4 g/m^2/day) and should take into account the following:

The total daily dose should be divided into equal amounts and given with each meal or feeding (e.g. three times to six times per day). Each dose should be rounded up to the nearest 0.1 ml for patients less than 2 years of age and 0.5 ml for patients 2 years of age and older.

Recommended starting dose in phenylbutyrate-naïve patients

- 8.5 ml/m^2/day (9.4 g/m^2/day) in patients with a body surface area (BSA) < 1.3 m^2
- 7 ml/m^2/day (8 g/m^2/day) in patients with a BSA ≥ 1.3 m^2

Initial dose in patients switching from sodium phenylbutyrate to RAVICTI

Patients switching from sodium phenylbutyrate to RAVICTI should receive the dose of RAVICTI that contains the same amount of phenylbutyric acid. The conversion is as follows:

- Total daily dose of RAVICTI (ml) = total daily dose of sodium phenylbutyrate tablets (g) x 0.86
- Total daily dose of RAVICTI (ml) = total daily dose of sodium phenylbutyrate powder (g) x 0.81

Initial dose in patients switching from sodium phenylacetate/sodium benzoate injection to RAVICTI

Once stable with controlled ammonia, patients switching from sodium phenylacetate/sodium benzoate to RAVICTI should receive a dose of RAVICTI at the higher end of the treatment range (11.2 ml/m^2/day) with measurements of plasma ammonia to guide further dosing.

The recommended daily dose schedule of 8.5 ml/m^2/day - 11.2 ml/m^2/day over a period of up to 24 hours for patients stabilised with no further hyperammonaemia is as follows:

- Step 1: 100% dose sodium phenylacetate/sodium benzoate and 50% dose of RAVICTI for 4-8 hours;
- Step 2: 50% dose sodium phenylacetate/sodium benzoate and 100% RAVICTI for 4-8 hours;
- Step 3: sodium phenylacetate/sodium benzoate discontinued and full dose RAVICTI continued according to feeding schedule for 4-8 hours.

For data regarding pharmacodynamic and pharmacokinetic properties in this age group, see sections 5.1 and 5.2.

Dose adjustment and monitoring in adults and children

The daily dose should be individually adjusted according to the patient's estimated urea synthetic capacity, if any, protein tolerance and the daily dietary protein intake needed to promote growth and development. Dietary protein is approximately 16% nitrogen by weight. Given that approximately 47% of dietary nitrogen is excreted as waste and approximately 70% of an administered 4-phenylbutyric acid (PBA) dose will be converted to urinary phenylacetylglutamine (U-PAGN), an initial estimated glycerol phenylbutyrate dose for a 24-hour period is 0.6 ml glycerol phenylbutyrate per gram of dietary protein ingested per 24 hour period assuming all the waste nitrogen is covered by glycerol phenylbutyrate and excreted as phenylacetylglutamine (PAGN).

Adjustment based on plasma ammonia

The dose of glycerol phenylbutyrate should be adjusted to produce a fasting plasma ammonia level that is less than half the upper limit of normal (ULN) in patients 6 years and older. In infants and young children (generally below 6 years of age) where obtaining fasting ammonia is problematic due to frequent feedings, the first ammonia of the morning should be kept below the ULN.

Adjustment based on urinary phenylacetylglutamine

U-PAGN measurements may be used to help guide glycerol phenylbutyrate dose adjustment and assess compliance. Each gram of U-PAGN excreted over 24 hours covers waste nitrogen generated from 1.4 grams of dietary protein. If U-PAGN excretion is insufficient to cover daily dietary protein intake and the fasting ammonia is greater than half the recommended ULN, the glycerol phenylbutyrate dose should be adjusted upward. The amount of dose adjustment should factor in the amount of dietary protein that has not been covered, as indicated by the 24-h U-PAGN level and the estimated glycerol phenylbutyrate dose needed per gram of dietary protein ingested.

Spot U-PAGN concentrations below the following levels may indicate improper medicinal product administration and/or lack of compliance:

- 9,000 microgram (mcg)/ml for patients under 2 years of age
- 7,000 microgram (mcg)/ml for patients ≥2 years of age with a BSA of ≤1.3

- 5,000 microgram (mcg)/ml for patients ≥2 years of age with a BSA of >1.3

If spot U-PAGN concentrations fall below these levels, assess compliance with medicinal product and/or effectiveness of medicinal product administration (e.g., via feeding tube) and consider increasing the glycerol phenylbutyrate dose in compliant patients to achieve optimal ammonia control (within normal limit for patients under 2 years of age and less than half ULN in older patients when fasted).

Adjustment based on plasma phenylacetate and phenylacetylglutamine
Symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness in the absence of high ammonia or intercurrent illness may be signs of phenylacetic acid (PAA) toxicity (see section 4.4, PAA toxicity). Therefore, measurement of plasma PAA and PAGN levels may be useful to guide dosing. The plasma PAA to PAGN (both measured in mcg/ml) ratio has been observed to be generally less than 1 in patients without PAA accumulation. In patients with a PAA to PAGN ratio exceeding 2.5, a further increase in glycerol phenylbutyrate dose may not increase PAGN formation, even if plasma PAA concentrations are increased, due to saturation of the conjugation reaction. In such cases, increasing the dosing frequency may result in a lower plasma PAA level and PAA to PAGN ratio. Ammonia levels must be monitored closely when changing the dose of glycerol phenylbutyrate.

N-acetylglutamate synthase (NAGS) and CITRIN (citrullinaemia type 2) deficiency
The safety and efficacy of RAVICTI for the treatment of patients with N-acetylglutamate synthase (NAGS) and CITRIN (citrullinaemia type 2) deficiency have not been established.

Paediatric population
Posology is the same for adult and paediatric patients.

Missed dose

Any missed dose should be taken as soon as recognised. However, if the next scheduled dose is within 2 hours for adults and within 30 minutes for children, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

Special populations

Elderly (65 years or older)
Clinical studies of RAVICTI did not include sufficient numbers of subjects ≥ 65 years of age to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other medicinal product therapy.

Hepatic impairment
Because conversion of PAA to PAGN occurs in the liver, patients with severe hepatic impairment may have reduced conversion capability and higher plasma PAA and plasma PAA to PAGN ratio. Therefore, dose for adult and paediatric patients with mild, moderate or severe hepatic impairment should be started at the lower end of the recommended dosing range (4.5 ml/m^2/day) and kept at the lowest dose necessary to control the patient's ammonia levels. A plasma PAA to PAGN ratio exceeding 2.5 may indicate saturation of PAA to PAGN conversion capacity and the need for reduced dosing and/or increased frequency of dosing. The plasma PAA to PAGN ratio may be useful in dose monitoring (see section 5.2).

Renal impairment
No studies were conducted in UCD patients with renal impairment; the safety of glycerol phenylbutyrate in patients with renal impairment is unknown. RAVICTI should be used with caution in patients with severe renal impairment. Preferably such patients should be started and maintained at the lowest dose necessary to control the blood ammonia levels.

Method of administration

Oral or gastroenteral use.

RAVICTI should be taken with meals and administered directly into the mouth via an oral syringe. The medicinal product should not be added or stirred into a large volume of other liquid, as glycerol phenylbutyrate is heavier than water and this may result in incomplete administration. Compatibility studies have been conducted (see section 4.5). RAVICTI may be added to a small amount of apple sauce, ketchup, or squash puree and should be used within 2 hours when stored at room temperature (25 °C). The medicinal product may be mixed with medical formulas (Cyclinex-1, Cyclinex-2, UCD-1, UCD-2, Polycose, Pro Phree and Citrulline) and used within 2 hours when stored at 25 °C, or up to 24 hours, refrigerated.

Patients should be advised that CE marked oral syringes compatible with the integrated syringe insert in the bottle, with suitable size for the prescribed dosing volume can be obtained from a pharmacy (see section 6.6).

The RAVICTI bottle should be opened by pushing down on the cap and twisting to the left. The tip of the oral syringe should be placed into the syringe insert and the bottle should be turned upside down with the syringe still inserted. The oral syringe should then be filled by pulling the plunger back until the syringe is filled with the prescribed amount of medicinal product. The oral syringe should be tapped to remove air bubbles, while making sure it is filled with the correct amount of liquid. The liquid can be swallowed from the oral syringe or the oral syringe can be attached to a gastrostomy or nasogastric tube. The same oral syringe should be used for all doses taken each day. It is important to ensure that the oral syringe is kept clean and dry between the dosing intervals. The oral syringe should not be rinsed between daily doses, as the presence of water causes glycerol phenylbutyrate to degrade. The bottle should be closed tightly after use. The oral syringe should be discarded after the last dose of the day.

RAVICTI may also be administered by CE marked medical grade silicone nasogastric or gastrostomy tube for those patients unable to take the medicinal product by mouth.

For additional information regarding method of administration and compatibility/in-use stability studies please refer to section 6.6.

Preparation for nasogastric tube or gastrostomy tube administration
In vitro studies evaluating the percent recovery of total dose delivered with nasogastric, nasojejunal or gastrostomy tubes demonstrated the percent of dose recovered was > 99% for doses ≥ 1 ml and 70% for a 0.5 ml dose. For patients who can swallow liquids take RAVICTI should be taken orally, even those with a nasogastric and/or gastrostomy tube. However, for patients who cannot swallow liquids, a nasogastric tube or gastrostomy tube may be used to administer RAVICTI as follows:

- An oral syringe should be utilised to withdraw the prescribed dose of RAVICTI from the bottle
- The tip of the oral syringe should be placed onto the tip of the gastrostomy/nasogastric tube
- The plunger of the oral syringe should be used to administer RAVICTI into the tube
- 10 ml of water or medical formula should be used to flush the tube once, and the flush should be allowed to drain after administration

It is not recommended to administer a dose of 0.5 ml or less with nasogastric, gastrostomy or nasojejunal tubes, given the low drug recovery in dosing.

4.3 Contraindications

- Hypersensitivity to the active substance.
- Treatment of acute hyperammonaemia.

4.4 Special warnings and precautions for use

Even while on treatment with glycerol phenylbutyrate, acute hyperammonaemia including hyperammonaemic encephalopathy may occur in a proportion of patients.

Reduced phenylbutyrate absorption in pancreatic insufficiency or intestinal malabsorption

Exocrine pancreatic enzymes hydrolyse glycerol phenylbutyrate in the small intestine, separating the active moiety, phenylbutyrate, from glycerol. This process allows phenylbutyrate to be absorbed into the circulation. Low or absent pancreatic enzymes or intestinal disease resulting in fat malabsorption may result in reduced or absent digestion of glycerol phenylbutyrate and/or absorption of phenylbutyrate and reduced control of plasma ammonia. Ammonia levels should be closely monitored in patients with pancreatic insufficiency or intestinal malabsorption.

Neurotoxicity

Reversible clinical manifestations suggestive of neurotoxicity (e.g., nausea, vomiting, somnolence) have been reportedly associated with phenylacetate levels ranging from 499-1,285 mcg/ml in cancer patients who received PAA intravenously. Although these have not been seen in clinical trials involving UCD patients, high PAA levels should be suspected in patients (particularly in children <2months) with unexplained somnolence, confusion, nausea and lethargy who have normal or low ammonia.

If symptoms of vomiting, nausea, headache, somnolence, confusion, or sleepiness are present in the absence of high ammonia or other intercurrent illnesses, measure plasma PAA and plasma PAA to PAGN, it should be considered to reduce the glycerol phenylbutyrate dose or increase the frequency of dosing if the PAA level exceeds 500 mcg/ml and the plasma PAA to PAGN ratio exceeds 2.5.

Monitoring and laboratory tests

The daily dose should be individually adjusted according to the patient's estimated urea synthetic capacity, if any, amino acid profile, protein tolerance and the daily dietary protein intake needed to promote growth and development. Supplemental amino acid formulations may be necessary to maintain essential amino acids and branched chain amino acids within normal range. Further adjustment may be based on monitoring of plasma ammonia, glutamine, U-PAGN and/or plasma PAA and PAGN as well as the ratio of plasma PAA to PAGN (see section 4.2).

Potential for other medicinal products to affect ammonia

Corticosteroids
Use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels. Monitor ammonia levels closely when corticosteroids and glycerol phenylbutyrate are used concomitantly.

Valproic acid and haloperidol
Hyperammonemia may be induced by haloperidol and by valproic acid. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in UCD patients.

Probenecid
Probenecid may inhibit the renal excretion of metabolites of glycerol phenylbutyrate including PAGN.

Women of childbearing potential/contraception in males and females

Effective contraceptive measures must be taken by women of child-bearing potential (see section 4.6).

Pregnancy

RAVICTI should not be used during pregnancy and in women of childbearing potential not using contraception unless the clinical condition of the woman requires treatment with glycerol phenylbutyrate, see section 4.6.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of medicinal products known to inhibit lipase should be given with caution as glycerol phenylbutyrate is hydrolysed by digestive lipase into phenylbutyrate acid and glycerol. This may be associated with increased risk of medicinal product interactions with lipase inhibitors and with lipase contained in pancreatic enzyme replacement therapies.

A potential effect on CYP2D6 isoenzyme cannot be excluded and caution is advised for patients who receive medicinal products that are CYP2D6 substrates.

Glycerol phenylbutyrate and/or its metabolites, PAA and PBA, have been shown to be weak inducers of CYP3A4 enzyme *in vivo*. *In vivo* exposure to glycerol phenylbutyrate has resulted in decreased systemic exposure to midazolam of approximately 32% and increased exposure to the 1-hydroxy metabolite of midazolam, suggesting that steady-state dosing of glycerol phenylbutyrate results in CYP3A4 induction. The potential for interaction of glycerol phenylbutyrate as a CYP3A4 inducer and those products predominantly metabolised by the CYP3A4 pathway is possible. Therefore, therapeutic effects and/or metabolite levels of medicinal products, including some oral contraceptives that are substrates for this enzyme may be reduced and their full effects cannot be guaranteed, following co-administration with glycerol phenylbutyrate.

Other medicinal products such as corticosteroids, valproic acid, haloperidol and probenecid may have the potential to affect ammonia levels, see section 4.4.

The effects of glycerol phenylbutyrate on cytochrome P450 (CYP) 2C9 isoenzyme and potential for interaction with celecoxib has been studied in humans with no evidence of an interaction observed.

Effects of glycerol phenylbutyrate on other CYP isoenzymes have not been studied in humans and cannot be excluded.

Compatibility studies have demonstrated glycerol phenylbutyrate chemical and physical in-use stability with the following foods and nutritional supplements: apple sauce, ketchup, squash puree, and five medical formulas (Cyclinex-1, Cyclinex-2, UCD-1, UCD-2, Polycose, Pro Phree and Citrulline) typically consumed by UCD patients (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

The use of RAVICTI in women of childbearing potential must be accompanied by the use of effective contraception (see section 4.4).

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data regarding the use of glycerol phenylbutyrate in pregnant women.
Glycerol phenylbutyrate should not be used during pregnancy and in women of childbearing potential not using contraception unless the clinical condition of the woman requires treatment with glycerol phenylbutyrate (see section 4.4).

Breast-feeding

It is unknown whether glycerol phenylbutyrate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from glycerol phenylbutyrate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats (see section 5.3). There are no data for human fertility.

4.7 Effects on ability to drive and use machines

RAVICTI may have major influence on the ability to drive and use machines given that treatment with glycerol phenylbutyrate may cause dizziness or headaches (see section 4.8). Patients should not drive or use machines whilst experiencing these adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions was based on exposure in 114 UCD patients (65 adults and 49 children between the ages of 2 months and 17 years) with deficiencies in CPS, OTC, ASS, ASL, ARG, or HHH across 4 short term and 3 long term clinical studies, in which 90 patients completed 12 months duration (median exposure = 51 weeks).

At the beginning of the treatment, abdominal pain, nausea, diarrhoea, and/or headache may occur; these reactions usually disappear within a few days even if treatment is continued. The most frequently reported adverse reactions (>5%) during glycerol phenylbutyrate treatment were diarrhoea, flatulence, and headache (8.8% each); decreased appetite (7.0%), vomiting (6.1%); and fatigue, nausea and, skin odour abnormal (5.3% each).

Additional adverse reactions have been evaluated in a clinical study including 16 UCD patients less than 2 months of age. The median exposure was 10 months (range 2 to 20 months).

Tabulated list of adverse reactions

The 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.

Any adverse reaction reported in one patient met the uncommon criteria. Due to the rarity of the UCD population, and the small size of the medicinal product safety population database (N=114), the adverse reaction frequency for rare and very rare is not known.

Table 1. List of adverse reactions

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Gastrointestinal viral infection
Endocrine disorders	Uncommon	Hypothyroidism
Metabolism and nutrition disorders	Common	Decreased appetite, increased appetite

	Uncommon	Hypoalbuminaemia, hypokalaemia
Psychiatric disorders	Common	Food aversion
Nervous system disorders	Common	Dizziness, headache, tremor
	Uncommon	Dysgeusia, lethargy, paraesthesia, psychomotor hyperactivity, somnolence, speech disorder
	Uncommon	Confusional state, depressed mood
Cardiac disorders	Uncommon	Ventricular arrhythmia
Vascular disorders	Uncommon	Hot flush
Respiratory, thoracic and mediastinal disorder	Uncommon	Dysphonia, epistaxis, nasal congestion, oropharyngeal pain, throat irritation
Gastrointestinal disorders	Common	Flatulence, diarrhoea, vomiting, nausea, abdominal pain, dyspepsia, abdominal distension, constipation, oral discomfort, retching
	Uncommon	Abdominal discomfort, abnormal faeces, dry mouth, eructation, defaecation urgency, upper abdominal pain and/or lower abdominal pain, painful defaecation, steatorrhoea, stomatitis
Hepatobiliary disorders	Uncommon	Gallbladder pain
Skin and subcutaneous tissue disorders	Common	Abnormal skin odour, acne
	Uncommon	Alopecia, hyperhidrosis, pruritic rash
Musculoskeletal and connective tissue disorders	Uncommon	Back pain, joint swelling, muscle spasm, pain in extremity, plantar fasciitis
Renal and urinary disorders	Uncommon	Bladder pain
Reproductive system and breast disorders	Common	Metrorrhagia
	Uncommon	Amenorrhoea, irregular menstruation
General disorders and administration site conditions	Common	Fatigue, oedema peripheral
	Uncommon	Hunger, pyrexia
Investigations	Common	Increased aspartate aminotransferase, alanine aminotransferase increased, increased anion gap, decreased lymphocyte count, decreased vitamin D
	Uncommon	Blood potassium increased, blood triglycerides increased, electrocardiogram abnormal, low density lipoprotein increased, prothrombin time prolonged, white blood cell count increased, weight increased, weight decreased

Paediatric population

Adverse reactions reported in more paediatric than adult patients during long-term treatment with glycerol phenylbutyrate included upper abdominal pain (3 of 49 paediatric [6.1%] versus 1 of 51 adults [2.0%] and increased anion gap (2 of 49 paediatric [4.1%] versus 0 of 51 adults [0%].

In an additional long term (24 month), uncontrolled, open-label clinical study the safety of RAVICTI has been evaluated in 16 UCD patients less than 2 months of age and 10 paediatric patients with UCDs aged 2 months to less than 2 years. The median exposure was 10 months (range 2 to 20 months) and

median exposure in the 2 months to less than 2 years of age was 9 months (range 0.2 to 20.3 months). Adverse reactions are summarized below.

Table 2. List of adverse reactions in patients less than 2 months of age

System organ class **Preferred Term**	**Total** **(N=16)**
Blood and lymphatic system disorders	**2 (12.5%)**
Anaemia,	1 (6.3%)
Thrombocytosis	1 (6.3%)
Metabolism and nutrition disorders	**1 (6.3%)**
Hypophagia	1 (6.3%)
Gastrointestinal disorders	**3 (18.8%)**
Diarrhoea,	2 (12.5%)
Constipation	1 (6.3%)
Flatulence	1 (6.3%)
Gastrooesophageal reflux disease	1 (6.3%)
Skin and subcutaneous tissue disorders	**3(18.8%)**
Rash	3(18.8%)
Investigations	**4 (25%)**
Amino acid level decreased	1 (6.3%)
Gamma-glutamyltransferase increased	1 (6.3%)
Hepatic enzyme increased	1 (6.3%)
Transaminases increased	1 (6.3%)

Table 3. List of adverse reactions in patients 2 months to less than 2 years of age

System Organ Class **Preferred Term**	**Total** **(N=10)**
Gastrointestinal disorders	**2 (20%)**
Constipation	1 (10%)
Diarrhoea	1 (10%)
Skin and subcutaneous tissue disorders	**2 (20%)**
Eczema	1 (10%)
Nail ridging	1 (10%)
Rash	1 (10%)

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

PAA, the active metabolite of glycerol phenylbutyrate, is associated with signs and symptoms of neurotoxicity (see section 4.4) and could accumulate in patients who receive an overdose. In case of overdose, the medicinal product should be discontinued and the patient monitored for any signs or symptoms of adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX09

Mechanism of action

Glycerol phenylbutyrate is a nitrogen-binding medicinal product. It is a triglyceride containing 3 molecules of PBA linked to a glycerol backbone.

UCDs are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia (NH_3, NH_4^+). Absence of these enzymes or transporters results in the accumulation of toxic levels of ammonia in the blood and brain of affected patients. Glycerol phenylbutyrate is hydrolysed by pancreatic lipases to yield, PBA, which is converted by beta oxidation to PAA, the active moiety of glycerol phenylbutyrate. PAA conjugates with glutamine (which contains 2 molecules of nitrogen) via acetylation in the liver and kidneys to form PAGN, which is excreted by the kidneys. On a molar basis, PAGN, like urea, contains 2 moles of nitrogen and provides an alternate vehicle for waste nitrogen excretion.

Pharmacodynamic effects

Pharmacological effects
In the pooled analysis of studies where patients switched from sodium phenylbutyrate to glycerol phenylbutyrate, ammonia $AUC_{0\text{-}24h}$ was 774.11 and 991.19 [(micromol/L)*hour] during treatment with glycerol phenylbutyrate and sodium phenylbutyrate, respectively (n = 80, ratio of geometric means 0.84; 95% confidence intervals 0.740, 0.949).

Cardiac electrophysiology
The effect of multiple doses of glycerol phenylbutyrate 13.2 g/day and 19.8 g/day (approximately 69% and 104% of the maximum recommended daily dose) on QTc interval was evaluated in a randomised, placebo- and active-controlled (moxifloxacin 400 mg), four-treatment-arm, crossover study in 57 healthy subjects. The upper bound of the one-sided 95% CI for the largest placebo-adjusted, baseline-corrected QTc, based on individual correction method (QTcI) for glycerol phenylbutyrate, was below 10 ms, demonstrating that glycerol phenylbutyrate had no QT/QTc prolonging effect. Assay sensitivity was confirmed by significant QTc prolongation of the positive control, moxifloxacin.

Clinical efficacy and safety

Clinical studies in adult patients with UCDs
Active-controlled, 4-week, noninferiority, blinded crossover study (Study 1)
A randomised, double-blind, active-controlled, crossover, noninferiority study (Study 1) compared equivalent doses of glycerol phenylbutyrate to sodium phenylbutyrate by evaluating 24-hour venous ammonia levels in patients with UCDs who had been on sodium phenylbutyrate prior to enrolment for control of their UCD. Patients were required to have a diagnosis of UCD involving deficiencies of CPS, OTC, or ASS, confirmed via enzymatic, biochemical, or genetic testing. Patients had to have no clinical evidence of hyperammonaemia at enrolment and were not allowed to receive medicinal products known to increase ammonia levels (e.g., valproate), increase protein catabolism (e.g., corticosteroids), or significantly affect renal clearance (e.g., probenecid).

Glycerol phenylbutyrate was non-inferior to sodium phenylbutyrate with respect to the 24-hour AUC for ammonia. Forty-four patients were evaluated in this analysis. Mean 24-hour AUCs for venous ammonia during steady-state dosing were 866 micromol/L*hour and 977 micromol/L*hour with glycerol phenylbutyrate and sodium phenylbutyrate, respectively (n = 44, ratio of geometric means 0.91; 95% confidence intervals 0.799, 1.034).

Consistent with plasma ammonia, blood glutamine levels were lower during glycerol phenylbutyrate treatment as compared with sodium phenylbutyrate in each arm of the crossover study (decrease of 44.3 ± 154.43 micromol/L after glycerol phenylbutyrate compared with NaPBA; p = 0.064, paired *t*-test; p = 0.048, Wilcoxon signed-rank test).

Open-label uncontrolled extension study in adults

A long-term (12-month), uncontrolled, open-label study (Study 2) was conducted to assess monthly ammonia control and hyperammonaemic crisis over a 12-month period. A total of 51 adult patients involving deficiencies of CPS, OTC, ASS, ASL, ARG, and HHH were enrolled in the study and all but 6 had been converted from sodium phenylbutyrate to equivalent doses of glycerol phenylbutyrate. Venous ammonia levels were monitored monthly. Mean fasting venous ammonia values in adults in Study 2 were within normal limits during long-term treatment with glycerol phenylbutyrate (range: 6-30 micromol/L). Of 51 adult patients participating in Study 2, 7 patients (14%) reported a total of 10 hyperammonaemic crises during treatment with glycerol phenylbutyrate as compared with 9 patients (18 %) who had reported a total of 15 crises in the 12 months prior to study entry while they were being treated with sodium phenylbutyrate.

Paediatric population

Clinical studies in paediatric patients with UCDs
The efficacy of glycerol phenylbutyrate in paediatric patients 2 months to 17 years of age involving deficiencies of OTC, ASS, ASL, and ARG was evaluated in 2 fixed sequence, open-label, sodium phenylbutyrate to equivalent dosing of glycerol phenylbutyrate switchover studies (Studies 3 and 4). Study 3 was 14 days in duration and Study 4 was 10 days in duration.

Glycerol phenylbutyrate was found to be non-inferior to sodium phenylbutyrate with respect to ammonia control in both of these paediatric studies. In the pooled analysis of the short-term studies in children (Study 3 and Study 4), plasma ammonia was significantly lower after switching to glycerol phenylbutyrate; ammonia $AUC_{0\text{-}24h}$ was 626.79 and 871.72 (micromol/L)*hour during treatment with glycerol phenylbutyrate and sodium phenylbutyrate, respectively (n = 26, ratio of geometric means 0.79; 95% confidence intervals 0.647, 0.955).

Mean blood glutamine levels were also non-significantly lower after glycerol phenylbutyrate treatment compared with sodium phenylbutyrate treatment by -45.2 ± 142.94 micromol/L (p = 0.135, paired *t*-test; p = 0.114, Wilcoxon signed-rank test).

Open-label, uncontrolled, extension studies in paediatric patients
Long-term (12-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonaemic crisis over a 12-month period in three studies (Study 2, which also enrolled adults, and extensions of Studies 3 and 4). A total of 49 children ages 2 months to 17 years with deficiencies of OTC, ASS, ASL, and ARG were enrolled, and all but 1 had been converted from sodium phenylbutyrate to glycerol phenylbutyrate. Mean fasting venous ammonia values were within normal limits during long-term treatment with glycerol phenylbutyrate (range: 17-25 micromol/L). Of the 49 paediatric patients who participated in these extension studies, 12 patients (25 %) reported a total of 17 hyperammonaemic crises during treatment with glycerol phenylbutyrate as compared with 38 crises in 21 patients (43 %) in the preceding 12 months prior to study entry, while they were being treated with sodium phenylbutyrate.

An open-label, long-term study (Study 5) was conducted to assess ammonia control in paediatric patients with UCD. The study enrolled a total of 45 paediatric patients between the ages of 1 and 17 years with UCD who had completed Study 2 and the safety extensions of Studies 3 and 4. The length of study participation ranged from 0.2 to 5.9 years. Venous ammonia levels were monitored at a minimum of every 6 months. Mean venous ammonia values in paediatric patients in Study 5 were within normal limits during long-term (24 months) treatment with glycerol phenylbutyrate (range: 15-25 micromol/L). Of the 45 paediatric patients participating in the open-label treatment with glycerol phenylbutyrate, 11 patients (24%) reported a total of 22 hyperammonemic crises.

In an additional long term (24 month), uncontrolled, open-label clinical study the safety of RAVICTI has been evaluated in 16 UCD patients less than 2 months of age and 10 paediatric patients with UCDs aged 2 months to less than 2 years.

Study in children less than 2 months of age

A total of 16 paediatric patients with UCDs aged less than 2 months participated in a long-term (24 months), uncontrolled, open-label study, of which 10 patients converted from sodium phenylbutyrate to RAVICTI. Three patients were treatment naïve and three additional patients were gradually discontinued from intravenous sodium benzoate and sodium phenylacetate while RAVICTI was initiated. All patients successfully transitioned to RAVICTI within 3 days, where successful transition was defined as no signs and symptoms of hyperammonemia and a venous ammonia value less than 100 micromol/L. The mean normalized venous ammonia values in paediatric patients aged less than 2 months were within normal limits during long-term treatment with glycerol phenylbutyrate (range: 35 to 94 micromol/L).

Hyperammonaemia was reported in 5 (50%) subjects age < 1 month (all serious but non-fatal) and 1 subject (16.7%) age 1-2 months (non-serious), which is consistent with more severe disease types diagnosed in the neonatal period. In 4 of the 5 subjects age < 1 month, possible risk factors included infectious precipitants, hyperammonaemic crisis at baseline, and missing dose. No precipitant trigger or missing dose was reported for the other 2 subjects (1 age < 1 month, 1 age 1-2 months). Dose adjustment was made to 3 subjects age < 1 month.

Study in children 2 months to less than 2 years of age
A total of 10 paediatric patients with UCDs aged 2 months to less than 2 years participated in a long term (24 months) uncontrolled, open label study, of which 6 patients converted from sodium phenylbutyrate to RAVICTI and 1 patient converted from sodium phenylbutyrate and sodium benzoate. Two patients were treatment naïve and one additional patient was gradually discontinued from intravenous sodium benzoate and sodium phenylacetate while RAVICTI was initiated.

Nine patients successfully transitioned to RAVICTI within 4 days, followed by 3 days of observation for a total of 7 days, where successful transition was defined as no signs and symptoms of hyperammonemia and a venous ammonia value less than 100 micromol/L. One additional patient developed hyperammonemia on day 3 of dosing and experienced surgical complications (bowel perforation and peritonitis) following jejunal tube placement on day 4. This patient developed hyperammonemic crisis on day 6, and subsequently died of sepsis from peritonitis unrelated to medicinal product. Although two patients had day 7 ammonia values of 150 micromol/L and 111 micromol/L respectively, neither had associated signs and symptoms of hyperammonemia.

Three patients reported a total of 7 hyperammonemic crises defined as having signs and symptoms consistent with hyperammonemia (such as frequent vomiting, nausea, headache, lethargy, irritability, combativeness, and/or somnolence) associated with high venous ammonia levels and requiring medical intervention. Hyperammonemic crises were precipitated by vomiting, upper respiratory tract infection, gastroenteritis, decreased caloric intake or had no identified precipitating event (3 events). There was one additional patient who had one venous ammonia level that exceeded 100 micromol/L which was not associated with a hyperammonemic crisis.

ADRs are summarised in section 4.8.

Reversal of the pre-existing neurological impairment is unlikely following treatment and neurological deterioration may continue in some patients.

5.2 Pharmacokinetic properties

Absorption

RAVICTI is a pro-drug of PBA. Upon oral ingestion, PBA is released from the glycerol backbone in the gastrointestinal tract by pancreatic lipases. PBA derived from glycerol phenylbutyrate is further converted by β-oxidation to PAA.

In healthy, fasting adult subjects receiving a single oral dose of 2.9 ml/m^2 of glycerol phenylbutyrate, peak plasma levels of PBA, PAA, and PAGN occurred at 2 h, 4 h, and 4 h, respectively. Upon single-dose administration of glycerol phenylbutyrate, plasma concentrations of PBA were quantifiable in 15

of 22 participants at the first sample time post dose (0.25 h). Mean maximum concentration (C_{max}) for PBA, PAA, and PAGN was 37.0 micrograms/ml, 14.9 micrograms/ml, and 30.2 micrograms/ml, respectively. In healthy subjects, intact glycerol phenylbutyrate was not detected in plasma.

In healthy subjects, the systemic exposure to PAA, PBA, and PAGN increased in a dose dependent manner. Following 4 ml of glycerol phenylbutyrate for 3 days (3 times a day [TID]), mean C_{max} and AUC were 66 mcg/ml and 930 mcg•h/ml for PBA and 28 microgram /ml and 942 mcg•h/ml for PAA, respectively. In the same study, following 6 ml of glycerol phenylbutyrate for 3 days (TID), mean C_{max} and AUC were 100 mcg/ml and 1,400 mcg•h/ml for PBA and 65 mcg/ml and 2,064 mcg•h/ml for PAA, respectively.

In adult UCD patients receiving multiple doses of glycerol phenylbutyrate, maximum plasma concentrations at steady state ($C_{max, ss}$) of PBA, PAA, and PAGN occurred at 8 h, 12 h, and 10 h, respectively, after the first dose in the day. Intact glycerol phenylbutyrate was not detectable in plasma in UCD patients.

Population pharmacokinetic modelling and dosing simulations suggest that PBA enters the circulation about 70-75% more slowly when given orally as glycerol phenylbutyrate as compared with sodium phenylbutyrate and further indicate that body surface area is the most significant covariate explaining the variability of PAA clearance.

Distribution

In vitro, the extent of human plasma protein binding for 14C-labeled metabolites was 80.6% to 98.0% for PBA (over 1-250 microgram/ml), and 37.1% to 65.6% for PAA (over 5-500 microgram/ml). The protein binding for PAGN was 7% to 12% and no concentration effects were noted.

Biotransformation

Upon oral administration, pancreatic lipases hydrolyse glycerol phenylbutyrate and release PBA. PBA undergoes β-oxidation to PAA, which is conjugated with glutamine in the liver and in the kidney through the enzyme phenylacetyl-CoA: Lglutamine- N-acetyltransferase to form PAGN. PAGN is subsequently eliminated in the urine.

Saturation of conjugation of PAA and glutamine to form PAGN was suggested by increases in the ratio of plasma PAA to PAGN with increasing dose and with increasing severity of hepatic impairment.

In healthy subjects, after administration of 4 ml, 6 ml, and 9 ml 3 times daily for 3 days, the ratio of mean AUC_{0-23h} of PAA to PAGN was 1, 1.25, and 1.6, respectively. In a separate study, in patients with hepatic impairment (Child-Pugh B and C), the ratios of mean values for PAA to PAGN among all patients dosed with 6 ml and 9 ml twice daily ranged from 0.96 to 1.28 and for patients dosed with 9 ml twice daily ranged from 1.18-3.19.

In *in vitro* studies, the specific activity of lipases for glycerol phenylbutyrate was seen in the following decreasing order: pancreatic triglyceride lipase, carboxyl ester lipase, and pancreatic lipase–related protein 2. Further, glycerol phenylbutyrate was hydrolysed *in vitro* by esterases in human plasma. In these *in vitro* studies, a complete disappearance of glycerol phenylbutyrate did not produce molar equivalent PBA, suggesting the formation of mono- or bis-ester metabolites. However, the formation of mono- or bis-esters was not studied in humans.

Elimination

The mean (SD) percentage of administered PBA eliminated as PAGN was approximately 68.9% (17.2) in adults and 66.4% (23.9) in paediatric UCD patients at steady state. PAA and PBA represented minor urinary metabolites, each accounting for <1% of the administered dose of PBA.

Special populations

Hepatic impairment
In a study in patients with clinically decompensated cirrhosis and hepatic encephalopathy (Child-Pugh B and C), mean C_{max} of PAA was 144 mcg/ml (range: 14-358 mcg/ml) after daily dosing of 6 ml of glycerol phenylbutyrate twice daily, while mean C_{max} of PAA was 292 mcg/ml (range: 57-655 mcg/ml) after daily dosing of 9 ml of glycerol phenylbutyrate twice daily. The ratio of mean values for PAA to PAGN among all patients dosed with 6 ml BID ranged from 0.96 to 1.28 and for patients dosed with 9 ml twice daily ranged from 1.18-3.19. After multiple doses, a PAA concentration >200 mcg/L was associated with a ratio of plasma PAA to PAGN concentrations higher than 2.5.

These findings collectively indicate that conversion of PAA to PAGN may be impaired in patients with severe hepatic impairment and that a plasma PAA to PAGN ratio > 2.5 identifies patients at risk of elevated PAA levels.

Renal impairment
The pharmacokinetics of glycerol phenylbutyrate in patients with impaired renal function, including those with end-stage renal disease (ESRD) or those on haemodialysis, have not been studied.

Gender
In healthy adult volunteers, a gender effect was found for all metabolites, with women generally having higher plasma concentrations of all metabolites than men at a given dose level. In healthy female volunteers, mean C_{max} for PAA was 51% and 120% higher than in male volunteers after administration of 4 ml and 6 ml 3 times daily for 3 days, respectively. The dose normalized mean AUC_{0-23h} for PAA was 108% higher in females than in males. However, dosing in UCD patients must be individualized based on the specific metabolic needs and residual enzyme capacity of the patient, irrespective of gender.

Paediatric population
Population pharmacokinetic modelling and dosing simulations suggest body surface area is the most significant covariate explaining the variability of PAA clearance. PAA clearance was 7.1 L/h, 10.9 L/h, 16.4 L/h, and 24.4 L/h, respectively, for UCD patients ages ≤ 2, 3 to 5, 6 to 11, and 12 to 17 years. In 16 paediatric UCD patients aged less than 2 months, PAA clearance was 3.8 L/h. In 7 paediatric patients aged 2 months to under 2 years of age who received RAVICTI for up to 12 months, the concentrations of PAA, PBA, and PAGN did not increase over the treatment period and the overall median PAA, PBA, and PAGN concentrations in these patients were similar to those observed in older paediatric age groups.

The mean peak ratio of PAA to PAGN in UCD patients aged birth to less than 2 months was higher (mean: 1.65; range 0.14 to 7.07) than for UCD patients aged 2 months to less than 2 years (mean 0.59; range 0.17 to 1.21). No PAA toxicity was observed in the subjects age < 2 months.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Carcinogenesis

In a rat study, glycerol phenylbutyrate caused a statistically significant increase in the incidence of pancreatic acinar cell adenoma, carcinoma, and combined adenoma or carcinoma in males and females, at a dose of 4.7 and 8.4 times the dose in adult patients, (6.87 ml/m^2/day based on combined AUCs for PBA and PAA). The incidence of the following tumours was also increased in female rats: thyroid follicular cell adenoma, carcinoma and combined adenoma or carcinoma, adrenal cortical combined adenoma or carcinoma, cervical schwannoma, uterine endometrial stromal polyp, and combined polyp or sarcoma.

Glycerol phenylbutyrate was not tumourigenic at doses up to 1,000 mg/kg/day in a 26 week mouse study.

Glycerol phenylbutyrate has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and shown no genotoxic activity.

Impairment of fertility

Glycerol phenylbutyrate had no effect on fertility or reproductive function in male and female rats at clinical exposure levels, however at oral doses up to approximately 7 times the dose in adult patients, maternal as well as male toxicity was observed and the number of nonviable embryos was increased.

Development studies

Oral administration of glycerol phenylbutyrate during the period of organogenesis in rats and rabbits had no effects on embryo-foetal development at 2.7 and 1.9 times the dose in adult patients, respectively. However, maternal toxicity and adverse effects on embryo-foetal development including reduced foetal weights and cervical ribs were observed in a rat study with a dose approximately 6 times the dose in adult patients, based on combined AUCs for PBA and PAA. No developmental abnormalities were observed in rats through day 92 postpartum following oral administration in pregnant rats, during organogenesis and lactation.

Juvenile animal study

In a juvenile rat study with daily oral dosing performed on postpartum day 2 through mating and pregnancy after maturation, terminal body weight was dose-dependently reduced in males and females, by up to 16% and 12% respectively. Fertility (number of pregnant rats) was decreased by up to 25%, at a dose of 2.6 times the dose in adult patients. Embryo toxicity (increased resorptions) and reduced litter size was also observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After the first opening of the bottle, the medicinal product must be used within 14 days and the bottle and its contents discarded, even if not empty.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear, Type III glass, bottle with a high density polyethylene (HDPE) child-resistant closure with integrated syringe insert.

Each bottle contains 25 ml of liquid.

Pack size: 1 bottle.

6.6 Special precautions for disposal and other handling

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

Based on prescribed dosing volume, patients should be advised to obtain CE marked oral syringes with suitable size for the dose and compatible with the syringe insert in the bottle from the pharmacy.

One oral syringe should be used each day. The oral syringe should not be rinsed between daily doses as the introduction of water causes glycerol phenylbutyrate to degrade. The oral syringe should be discarded after the last dose of each day.

Chemical compatibility of glycerol phenylbutyrate with medical grade silicone nasogastric, gastrostomy, and nasojejunal tubes has been demonstrated. *In vitro* studies evaluating the percent recovery of total dose delivered with nasogastric or gastrostomy tubes demonstrated the percent of dose recovered was >99% for doses > 1 ml and 70% for a 0.5 ml dose. Therefore, it is recommended that nasogastric, nasojejunal or gastrostomy tubes only be used to administer doses $\geq$ 1 ml. If there is a need to administer a dose of 0.5 ml or less with such nasogastric, gastrostomy or nasojejunal tubes, consideration should be given to the low drug recovery in dosing.

7. MARKETING AUTHORISATION HOLDER

Immedica Pharma AB
SE-113 63 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1062/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 November 2015
Date of latest renewal: 25/08/2020

10. DATE OF REVISION OF THE TEXT

05/12/2025

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

Unimedic AB
Storjordenvägen 2
SE-864 31 Matfors
Sweden

Patheon France
40 Boulevard de Champaret
38300 Bourgoin Jallieu
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RAVICTI 1.1 g/ml oral liquid
glycerol phenylbutyrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 1.1 g of glycerol phenylbutyrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oral liquid
1 bottle of 25 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral or gastroenteral use.

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
Use within 14 days of opening.

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Immedica Pharma AB
SE-113 63 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1062/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RAVICTI

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

RAVICTI 1.1 g/ml oral liquid
glycerol phenylbutyrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 1.1 g of glycerol phenylbutyrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Oral liquid
25 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral or gastroenteral use.

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
Use within 14 days of opening.

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Immedica Pharma AB
SE-113 63 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1062/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

RAVICTI 1.1 g/ml oral liquid
glycerol 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 RAVICTI is and what it is used for

RAVICTI contains the active substance 'glycerol phenylbutyrate' which is used to treat six known 'urea cycle disorders' (UCDs) in adults and children. The UCDs include deficiencies of certain liver enzymes such as carbamoyl phosphate synthetase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH).

RAVICTI must be combined with a diet reduced in protein intake, and in some cases a diet with supplements such as essential amino acids (arginine, citrulline, protein-free calorie supplements).

About urea cycle disorders
- In urea cycle disorders, the body cannot remove the nitrogen from the protein that we eat.
- Normally, the body turns the extra nitrogen in the protein into a waste compound called 'ammonia'. The liver then removes ammonia from the body through a cycle called the 'urea cycle'.
- In urea cycle disorders, the body is not able to produce enough liver enzymes to remove the extra nitrogen.
- This means that ammonia builds up in the body. If ammonia is not removed from the body, it can harm the brain and lead to low levels of consciousness or coma.
- Urea cycle disorders are rare.

How RAVICTI works
RAVICTI helps the body to eliminate waste nitrogen. This reduces the amount of ammonia in your body.

2. What you need to know before you take RAVICTI

Do not take RAVICTI
- if you are allergic to glycerol phenylbutyrate

- if you have acute hyperammonaemia (high levels of ammonia in your blood), which requires more rapid intervention (see section "Warnings and precautions")

If you are not sure if the above apply to you, talk to your doctor or pharmacist before taking RAVICTI.

Warnings and precautions
Talk to your doctor or pharmacist before taking RAVICTI:
- if you have problems with your kidneys or liver - this is because RAVICTI is removed from your body through the kidneys and liver
- if you have problems with your pancreas, stomach or gut ('intestines') - these organs are responsible for absorption of RAVICTI into the body

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking RAVICTI.

In some cases such as infection or post-surgery, the amount of ammonia may go up despite treatment with this medicine and may damage the brain (hyperammonaemic encephalopathy).

In other cases the amount of ammonia in the blood goes up quickly. In this case, RAVICTI will not stop the level of ammonia in your blood from becoming seriously high.
High levels of ammonia leads to feeling sick (nausea), being sick (vomiting) or feeling confused.
Tell your doctor or go to the hospital straight away if you notice any of these signs.

Laboratory tests will be needed so your doctor can determine and maintain the correct dose for you.

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

In particular, tell your doctor or pharmacist if you are taking any of the following medicines, which may be less effective when used with RAVICTI. If you take these medicines, you may need regular blood tests:
- midazolam and barbiturates - used for sedation, trouble sleeping or epilepsy
- contraceptives

Also, tell your doctor if you are taking the following medicines as they may increase the amount of ammonia in your body or change how RAVICTI works:
- corticosteroids - used to treat inflamed areas of the body
- valproate - a medicine for epilepsy
- haloperidol - used to treat some mental health problems
- probenecid - to treat high levels of uric acid in the blood which can cause gout ('hyper-uricaemia')
- lipase inhibitors (such as orlistat) – used to treat obesity
- lipase in pancreatic replacement therapies

If any of the above apply to you (or you are not sure), talk to your doctor before taking RAVICTI.

Pregnancy, contraception and breast-feeding
- If you are pregnant, tell your doctor before you start taking RAVICTI. If you become pregnant while taking RAVICTI, talk to your doctor. RAVICTI should not be used during pregnancy, as a risk for your unborn baby cannot be excluded.
- If you are a woman who could become pregnant, you must use an effective method of contraception, during treatment with RAVICTI. Talk to your doctor about the best method of contraception for you.

- You should discuss with your physician before you plan to breast-feed while taking RAVICTI. A decision should be made whether to breast-feed or stop taking RAVICTI taking into account the benefit of the treatment for you and the benefit of breast-feeding for your baby. This is because RAVICTI may pass into breast milk and a risk to the newborn/infant cannot be excluded.

Driving and using machines
RAVICTI may have major influence on the ability to drive and use machines. When taking RAVICTI you may feel dizzy or have a headache. Do not drive or use machines whilst experiencing these side effects.

3. How to take RAVICTI

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

You must follow a special low protein diet during treatment with RAVICTI.
- This diet will be designed for you by your doctor and dietician.
- You must follow this diet carefully.
- You may need to take supplemental amino acid formulations.
- You will need to have treatment and to follow a diet throughout your life, unless you have a successful liver transplantation.

How much to take
Your doctor will tell you how much RAVICTI you should take each day.
- Your daily dose will depend on your size and weight, the amount of protein in your diet, and your overall urea cycle disorder condition.
- Your doctor may give you a lower dose if you have kidney or liver problems.
- You will need regular blood tests so your doctor can determine the correct dose for you.
- Your doctor might tell you to take RAVICTI more than 3 times each day. In small children, this may be 4 to 6 times a day. There must be at least 3 hours between each dose.

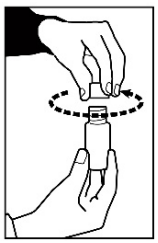
Taking this medicine
Your doctor will tell you how to take RAVICTI oral liquid. It can be taken in the following ways:
- by mouth
- through a tube that goes through your tummy (‘abdomen’) to the stomach - called a ‘gastrostomy tube’
- through a tube that goes through your nose to the stomach - called a ‘nasogastric tube’

Take RAVICTI by mouth unless otherwise directed by your doctor.

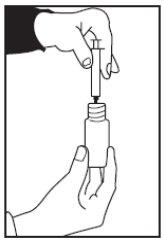
RAVICTI and meals
Take RAVICTI with or straight after a meal. Young children should be given the medicine during or straight after a feeding.

Measuring the dose
- Use an oral syringe to measure your dose.
- You should have the RAVICTI bottle along with an oral syringe to administer the correct amount of RAVICTI.

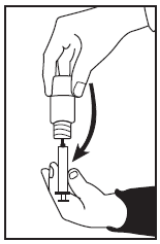
1. Open the bottle of RAVICTI by pushing down on the cap and twisting to the left.



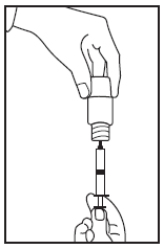
2. Place the tip of the oral syringe into integrated syringe insert in the bottle.



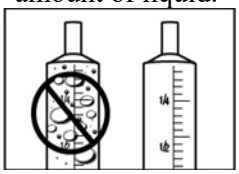
3. Turn the bottle upside down with the oral syringe still inserted.



4. Fill the oral syringe by pulling the plunger back until the syringe is filled with the amount of RAVICTI liquid that your doctor has told you to take.
   - Note: If possible, use the oral syringe ml size that is nearest to (but not smaller than) the recommended dose (for example, if the dose is 0.8 ml, use a 1 ml oral syringe).



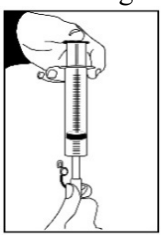
5. Tap the oral syringe to remove air bubbles, making sure you have filled it with the correct amount of liquid.



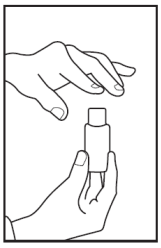
6. Swallow the liquid from the oral syringe or attach the oral syringe to a gastrostomy or nasogastric tube.

7. **Important note:** Do not add or stir RAVICTI into larger volumes of liquid such as water or juice as RAVICTI is heavier than most liquids. Mixing RAVICTI with large volumes of liquid may result in you not getting the full dose.
8. RAVICTI can be added to a small amount of soft foods, such as ketchup, medical formulas, apple sauce or squash puree.

9. If the volume of your oral syringe is smaller than your prescribed dose, you will have to repeat these steps to get your full dose. Use one oral syringe for all doses taken each day.
10. After you take your full dose, have a drink of water to make sure no medicine is left in your mouth, or flush the gastrostomy or nasogastric tube with 10 ml of water using a new oral syringe. The syringe used to flush the gastrostomy or nasogastric tube shall not be used for measuring the dose of RAVICTI to avoid introduction of water into the medicine.



11. Close the bottle by screwing on the cap.



12. **Important note:** Do not rinse the the oral syringe between daily doses as the introduction of water causes RAVICTI to degrade. If RAVICTI gets in contact with water, the liquid will become cloudy in appearance. Store bottle and oral syringe in a clean, dry place between doses.
13. Discard the oral syringe after the last dose of the day. Do not re-use the oral syringe for measuring the dose of RAVICTI on another day.
14. Remaining unused syringes should be kept for use with another bottle. Each bottle should be discarded after 14 days.

If you take more RAVICTI than you should
If you take more of this medicine than you should, talk to a doctor.

If you notice any of the following signs, talk to a doctor or go to a hospital straight away as these may be signs of overdose or high ammonia:
- feeling sleepy, tired, light-headed or sometimes confused
- headache
- changes in taste
- problems hearing
- feeling disorientated
- less able to remember things
- existing neurological conditions may get worse

If you forget to take RAVICTI
If you forget a dose, take the missed dose as soon as you remember. However, for adults, if the next dose is in less than 2 hours, then skip it and take your next dose as normal.
For children: if the next dose is in less than 30 minutes, then skip it and give the next dose as normal.
- 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.

If you stop taking RAVICTI
You will need to take this medicine and follow a special low protein diet throughout your life. Do not stop taking RAVICTI without talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Tell your doctor or pharmacist if you notice any side effects.
The following side effects may happen with this medicine:

Common: may affect up to 1 in 10 people
- stomach bloating or pain, constipation, diarrhoea, heartburn, wind, vomiting, feeling sick (nausea), pain in the mouth, retching
- swelling of the hands or feet, feeling tired
- feeling dizzy, headache or tremor
- decreased or increased appetite
- not wanting to eat some foods
- bleeding between menstrual periods
- acne, skin smells abnormal
- tests show increased liver enzyme levels, imbalance of salts in the blood, low levels of a type of white blood cell ('lymphocytes') or low levels of vitamin D

Uncommon: may affect up to 1 in 100 people
- dry mouth, burping, stomach ache or discomfort, changes in your stools such as being oily, urgent need for bowel movements, painful bowel movements, inflammation of mouth and lips
- feeling hungry, increased temperature
- hot flushes
- gallbladder pain
- bladder pain
- back pain, joint swelling, muscle spasms, pain in the arms or legs, heel spur
- viral infection in the gut
- feeling of pins and needles, feeling very restless, sleepiness, feeling drowsy, problems with speech, feeling confused, feeling depressed, alteration of taste
- menstrual periods stop or are irregular
- voice disorder, nosebleeds, stuffy nose, sore or painful throat
- hair loss, sweating more than usual, itchy rash,
- uneven heartbeat
- reduced thyroid function
- weight loss or weight gain
- tests show higher or lower potassium in your blood
- tests show higher levels of triglycerides, low density lipo-protein or white cells in your blood
- tests show abnormal ECG ('electrocardiogram')
- tests show prothrombin time is longer
- tests show low albumin in your blood

Side effects in children less than 2 months of age
The following side effects have been observed in a clinical study including 16 patients less than 2 months of age:
- diarrhoea, constipation, wind, reflux of stomach contents, poor feeding
- rash
- reduced number of red blood cells
- increased number of platelets (may cause blood clot)
- increased liver enzymes
- decreased amino acid levels

Side effects in children 2 months to less than 2 years of age
- diarrhoea, constipation
- eczema, nail ridging, rash

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 RAVICTI

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

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

This medicinal product does not require any special storage conditions. Once the bottle is open, you must use your medicine within 14 days of opening. The bottle should be discarded even if it is not empty.

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 RAVICTI contains
- The active substance is glycerol phenylbutyrate.
- Each ml of liquid contains 1.1 g of glycerol phenylbutyrate. This corresponds to a density of 1.1 g/ml.
- There are no other ingredients.

What RAVICTI looks like and contents of the pack
The liquid is filled into a 25 ml clear glass bottle and capped with a plastic, child-resistant cap.
In order to ensure correct dosing of RAVICTI, CE-marked oral syringes with suitable size for the dose and compatible with the syringe insert can be obtained from the pharmacy. Ask your doctor or pharmacist which type of syringes you need to obtain based on the prescribed dose volume.

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SE-113 63 Stockholm
Sweden

Manufacturer

Unimedic AB
Storjordenvägen 2
SE-864 31 Matfors
Sweden

Patheon France
40 Boulevard de Champaret
38300 Bourgoin Jallieu
France

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.