1. NAME OF THE MEDICINAL PRODUCT

RAVICTI 1.1 g/ml

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

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.

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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/L 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.

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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	Uncommon	Dysphonia, epistaxis, nasal congestion,

mediastinal disorder		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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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

The expiry date of the product is indicated on the packaging materials.

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

To be stored at no more than 25°C.

6.5 Nature and contents of container

Clear, Type III glass, bottle with a high density polyethylene (HDPE) child-resistant closure
Each bottle contains 25 ml of liquid.

Pack size: 1 bottle and 1 reclosable bottle cap adapter per carton.

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.

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.

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9.Registration number: 162-79-35361

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תאריך עדכון העלון	פרקים שהתעדכנו	אסמכתא לעלון	הערות
04/2023	אישור הרחבת ההתוויה בתאריך 12/02/2023 **4.1 Therapeutic indications** **4.4 Special warnings and precautions for use** **4.6 Fertility, pregnancy and lactation** **4.8 Undesirable effects** **5.1 Pharmacodynamic properties** **5.2 Pharmacokinetic properties** **6.5 Nature and contents of container** **6.6 Special precautions for disposal and other handling** **8. Manufacturer:**	EMA published 20/10/2022	