Health and Social Care Board

Interface Pharmacist Network Specialist Medicines

# Glycerol phenylbutyrate (Ravicti®)

## used in Urea Cycle Disorder

## GP Information Sheet

### Introduction

A urea cycle disorder is a genetic disorder caused by a mutation that results in a deficiency of one of the six enzymes in the urea cycle. These enzymes are responsible for removing ammonia from the blood stream. The urea cycle involves a series of biochemical steps in which nitrogen, a waste product of protein metabolism, is removed from the blood and converted to urea in the blood. Normally, the urea is transferred into the urine and removed from the body. In urea cycle disorders, the nitrogen accumulates in the form of ammonia, resulting in hyperammonaemia which can cause irreversible brain damage, coma and/or death. The onset and severity of urea cycle disorders is highly variable. This depends on the specific mutation involved and correlates with the amount of urea cycle enzyme function. Severe mutations result in very little enzyme function and ability to detoxify ammonia, and cause severe urea cycle disorders. Mild to moderate mutations provide some ability to detoxify ammonia, and result in mild to moderate urea cycle disorders.

Glycerol phenylbutyrate is a nitrogen-binding medicinal product. It is a triglyceride. It is indicated for use as adjunctive therapy for chronic management of adult and paediatric patients with urea cycle disorders (UCDs). It is used with dietary protein restriction and in some cases, dietary supplements (e.g. essential amino acids, arginine, protein-free calorie supplements).

### Dosage and administration

Adults and children aged ≥ 2 months to 18 years of age:

| Recommended starting dosage in phenylbutyrate-naïve patients | Dose ($g/m^2/day$) | Volume of product for this dose ($ml/m^2/day$) |
|---|---|---|
| • in patients with a body surface area (BSA) < 1.3 $m^2$ | 9.4 | 8.5 |
| • in patients with a BSA ≥ 1.3 $m^2$ | 8 | 7 |
| Recommended total daily dose range | 5.3 - 12.4 | 4.5 - 11.2 |

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 0.5 ml.

Doses should be taken with meals and administered directly into the mouth via an oral syringe. It 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.

The recommended dosages for patients naïve to glycerol phenylbutyrate and for patients switching from sodium phenylbutyrate to glycerol phenylbutyrate are different. Patients switching should receive the dosage of that contains the same amount of phenylbutyric acid. The conversion and dose will be advised by the specialist.

The daily dose is 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.

Dose is adjusted based on plasma ammonia, glutamine and/or on urinary phenylacetylglutamine measurements which are undertaken at the specialist's clinic.

## Available as

Ravicti® 1.1 g/ml oral liquid. Each ml of liquid contains 1.1g of glycerol phenylbutyrate.
Each bottle contains 25 ml of liquid. Each bottle should be discarded after 3 days of use even if not empty, and one oral syringe should be used each day.
Starter pack sizes are available containing either 1ml, 3ml or 5ml oral syringes as below:
• One 25ml bottle, one reclosable bottle cap adapter and seven 1ml oral syringes
• One 25ml bottle, one reclosable bottle cap adapter and seven 3ml oral syringes
• One 25ml bottle, one reclosable bottle cap adapter and seven 5ml oral syringes
These syringe sizes are appropriate for the possible range of starting doses.

## Monitoring requirements

Review and monitoring is performed by the specialist at clinic appointments which are generally every 6 months in stable adult patients.
This involves assessment of the patient's estimated urea synthetic capacity, protein requirement, dietary protein intake, need for supplemental amino acid formulations, measurement of plasma ammonia and other makers to determine the response to treatment and guide treatment adjustments. Serum potassium is monitored periodically as renal excretion of phenylglutamine may induce urinary loss of potassium.

## Adverse effects, precautions and contraindications

- Commonly reported adverse effects include gastrointestinal disorders, abnormal skin odour, and acne.
- Dizziness, headache, and tremor are also commonly reported. In some cases, if these are are not explained by other concurrent illnesses, measurement of levels of ammonia and related metabolites and dosage adjustment of glycerol phenylbutyrate may be required by the specialist.
- Uncommonly reported include: hypothyroidism, hypoalbuminaemia, hypokalaemia and hyperkalaemia, increased triglycerides, abnormal LDL, prolonged prothrombin time, increased white cell count, electrocardiogram changes, gallbladder pain, alopecia, hyperhidrosis, pruritic rash, back pain, bladder pain, joint swelling, and muscle spasm.

## Common drug interactions

- Corticosteroids: use of corticosteroids may cause the breakdown of body protein and increase plasma ammonia levels. Steroids should be used with caution in patients with a urea cycle disorder. Metabolic decompensation and hyperammonaeima has been reported in patients with a urea cycle disorder prescribed steroids. Ammonia levels should be monitored closely if steroid treatment is necessary in patients with a urea cycle defect.
- Valproic acid and haloperidol: hyperammonaemia may be induced by haloperidol and by valproic acid. Valporic acid and haloperidol should be used with caution in patients with a urea cycle disorder. Monitor ammonia levels closely if use of valproic acid or haloperidol is necessary in patients with a urea cycle disorder.
- Probenecid: may inhibit the renal excretion of metabolites of glycerol phenylbutyrate
- Lipase contained in pancreatic enzyme replacement therapies and lipase inhibitors (e.g. Orlistat). Malabsorption may result in reduced or absent digestion of glycerol phenylbutyrate and/or absorption of phenylbutyrate and reduced control of plasma ammonia.
- Glycerol phenylbutyrate is a weak inducer of CYP3A4 enzyme in vivo. The potential for interaction with other products predominantly metabolised by the CYP3A4 pathway is possible, and significance of this may vary depending on the drugs involved.

## Communication

For any queries relating to this patient's treatment with glycerol phenylbutyrate, please contact the specialist.


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