Health and Social Care Board

Interface Pharmacist Network Specialist Medicines

Sodium phenylbutyrate

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.

Sodium phenylbutyrate is rapidly metabolized to phenylacetate, which conjugates with glutamine to form phenylacetylglutamine. Phenylacetylglutamine then is excreted by the kidneys. On a molar basis, it is comparable to urea (each containing two moles of nitrogen) and therefore provides an alternate vehicle for waste nitrogen excretion.

Sodium phenylbutyrate is indicated as adjunctive therapy in the management of adult and children with urea cycle disorders. It is used with dietary protein restriction and in some cases, dietary supplements (e.g. essential amino acids, and protein-free calorie supplements).

Dosage and Administration

The usual **total daily dose** is:

Neonates, infants and children < 20 kg:	450 - 600 mg/kg/day
Children > 20 kg, adolescents and adults:	9.9 - 13.0 g/m^2/day

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).

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.

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

Caution: Sodium intake should be considered in heart failure or renal insufficiency.

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

Available as

Ammonaps® tablets 500mg.
Pheburane ® granules 483mg/g.
Ammonaps ® granules 940 mg/g. Three measuring spoons of different measures are provided. This will give the following doses; small (white) measure 1.2 g, medium (yellow) measure 3.3 g and large (blue) measure 9.7 g of sodium phenylbutyrate.

The granules should be mixed with solid foods (such as mashed potatoes or apple sauce) or liquid foods (such as water, apple juice, orange juice or protein-free infant formulas).

Preparations contain significant amounts of sodium. Each tablet contains 62 mg of sodium. Each gram of sodium phenylbutyrate granules contains 124 mg.

Monitoring Requirements

Review and monitoring is performed by the specialist at clinic appointments which is 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 and 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 phenylacetylglutamine may induce a urinary loss of potassium.

Adverse Effects, Precautions and Contraindications

- Sodium phenylbutyrate is contraindicated in pregnancy or while breast feeding. However cessation of sodium phenylbutyrate in a patient prescribed sodium phenylbutyrate for a urea cycle disorder should only occur in consultation with a patient's specialist.
- Very common: amenorrhoea, irregular menstruation.
- Common: anaemia, thrombocytopenia, leukopenia, leucocytosis, thrombocytosis; metabolic acidosis, alkalosis, decreased appetite; decreased blood potassium, albumin, total protein and phosphate; decreased blood alkaline phosphatase, transaminases, bilirubin, uric acid, chloride, phosphate and sodium; increased weight, rash, abnormal skin odour, abdominal pain, vomiting, nausea, constipation, dysgeusia, oedema, syncope, headache, depression, and irritability.
- Uncommon: aplastic anaemia, ecchymosis, arrhythmia, pancreatitis, peptic ulcer, rectal haemorrhage, and gastritis.

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 hyperammonaemia have 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.
- Valproic acid and haloperidol: hyperammonaemia may be induced by haloperidol and by valproic acid. Valproic acid and haloperidol should be used in caution in patients with a urea cycle disorder. Monitor ammonia levels closely when use of valproic acid or haloperidol is necessary in UCD patients.
- Probenecid: may inhibit the renal excretion of the conjugation product of sodium phenylbutyrate.

Communication

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

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC or the BNF

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