

1. NAME OF THE MEDICINAL PRODUCT

AMMONAPS 500 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg sodium phenylbutyrate.

Excipient(s) with known effect

Each tablet contains 2.7 mmol (62 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

The tablets are off-white, oval and embossed with “UCY 500”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMMONAPS is indicated as adjunctive therapy in the chronic management of urea cycle disorders, involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or argininosuccinate synthetase.

It is indicated in all patients with *neonatal-onset* presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with *late-onset* disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy.

4.2 Posology and method of administration

AMMONAPS treatment should be supervised by a physician experienced in the treatment of urea cycle disorders.

The use of AMMONAPS tablets is indicated for adults and children who are able to swallow tablets. AMMONAPS is also available as granules for infants, children who are unable to swallow tablets and for patients with dysphagia.

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

The usual total daily dose of sodium phenylbutyrate in clinical experience is:

- 450 - 600 mg/kg/day in children weighing less than 20 kg
- 9.9 - 13.0 g/m²/day in children weighing more than 20 kg, adolescents and adults.

The safety and efficacy of doses in excess of 20 g/day (40 tablets) have not been established.

Therapeutic monitoring: Plasma levels of ammonia, arginine, essential amino acids (especially branched chain amino acids), carnitine and serum proteins should be maintained within normal limits. Plasma glutamine should be maintained at levels less than 1,000 µmol/l.

Nutritional management: AMMONAPS must be combined with dietary protein restriction and, in some cases, essential amino acid and carnitine supplementation.

Citrulline or arginine supplementation is required for patients diagnosed with *neonatal-onset* form of carbamyl phosphate synthetase or ornithine transcarbamylase deficiency at a dose of 0.17 g/kg/day or 3.8 g/m²/day.

Arginine supplementation is required for patients diagnosed with deficiency of argininosuccinate synthetase at a dose of 0.4 - 0.7 g/kg/day or 8.8 - 15.4 g/m²/day.

If caloric supplementation is indicated, a protein-free product is recommended.

The total daily dose of AMMONAPS should be divided into equal amounts and given with each meal (e.g. three times per day). The tablets should be taken with a large volume of water.

4.3 Contraindications

- Pregnancy.
- Breast-feeding.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

AMMONAPS tablets should not be used in patients with dysphagia due to the potential risk of oesophageal ulceration if tablets are not promptly delivered to the stomach.

This medicinal product contains 62 mg sodium per tablet, equivalent to 3% of the WHO recommended maximum daily intake for sodium.

The maximum recommended daily dose of this product contains 2.5 g sodium which is equivalent to 124% of the WHO recommended maximum daily intake for sodium.

AMMONAPS is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

AMMONAPS should therefore be used with caution in patients with congestive heart failure or severe renal insufficiency, and in clinical conditions where there is sodium retention with oedema.

Since the metabolism and excretion of sodium phenylbutyrate involves the liver and kidneys, AMMONAPS should be used with caution in patients with hepatic or renal insufficiency.

Serum potassium should be monitored during therapy since renal excretion of phenylacetylglutamine may induce a urinary loss of potassium.

Even on therapy, acute hyperammonaemic encephalopathy may occur in a number of patients.

AMMONAPS is not recommended for the management of acute hyperammonaemia, which is a medical emergency.

In children unable to swallow tablets, it is recommended to use AMMONAPS granules instead.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of probenecid may affect renal excretion of the conjugation product of sodium phenylbutyrate.

There have been published reports of hyperammonaemia being induced by haloperidol and by valproate. Corticosteroids may cause the breakdown of body protein and thus increase plasma ammonia levels. More frequent monitoring of plasma ammonia levels is advised when these medications have to be used.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies has shown reproductive toxicity, i.e. effects on the development of the embryo or the foetus. Prenatal exposure of rat pups to phenylacetate (the active metabolite of phenylbutyrate) produced lesions in cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number. The significance of these data in pregnant women is not known; therefore the use of AMMONAPS is contra-indicated during pregnancy (see section 4.3).

Effective contraceptive measures must be taken by women of child-bearing potential.

Lactation

When high doses of phenylacetate (190 - 474 mg/kg) were given subcutaneously to rat pups, decreased proliferation and increased loss of neurons were observed, as well as a reduction in CNS myelin. Cerebral synapse maturation was retarded and the number of functioning nerve terminals in the cerebrum was reduced, which resulted in impaired brain growth. It has not been determined if phenylacetate is secreted in human milk and therefore the use of AMMONAPS is contra-indicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In clinical trials with AMMONAPS, 56 % of the patients experienced at least one adverse event and 78 % of these adverse events were considered as not related to AMMONAPS.

Adverse reactions mainly involved the reproductive and gastrointestinal system.

The adverse reactions are listed below, by system organ class and by frequency. Frequency is defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Common: Anaemia, thrombocytopenia, leukopenia, leukocytosis, thrombocytosis

Uncommon: Aplastic anaemia, ecchymosis

Metabolism and nutrition disorders

Common: Metabolic acidosis, alkalosis, decreased appetite

Psychiatric disorders

Common: Depression, irritability

Nervous system disorders

Common: Syncope, headache

Cardiac disorders

Common: Oedema

Uncommon: Arrhythmia

Gastrointestinal disorders

Common: Abdominal pain, vomiting, nausea, constipation, dysgeusia

Uncommon: Pancreatitis, peptic ulcer, rectal haemorrhage, gastritis

Skin and subcutaneous tissue disorders

Common: Rash, abnormal skin odour

Renal and urinary disorders

Common: Renal tubular acidosis

Reproductive system and breast disorders

Very common: Amenorrhoea, irregular menstruation

Investigations

Common: Decreased blood potassium, albumin, total protein and phosphate. Increased blood alkaline phosphatase, transaminases, bilirubin, uric acid, chloride, phosphate and sodium. Increased weight.

A probable case of toxic reaction to AMMONAPS (450 mg/kg/d) was reported in an 18-year old anorectic female patient who developed a metabolic encephalopathy associated with lactic acidosis, severe hypokalaemia, pancytopenia, peripheral neuropathy, and pancreatitis. She recovered following dose reduction except for recurrent pancreatitis episodes that eventually prompted treatment discontinuation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system](#) listed in [Appendix V](#).

4.9 Overdose

One case of overdose occurred in a 5-month old infant with an accidental single dose of 10 g (1370 mg/kg). The patient developed diarrhoea, irritability and metabolic acidosis with hypokalaemia. The patient recovered within 48 hours after symptomatic treatment.

These symptoms are consistent with the accumulation of phenylacetate, which showed dose-limiting neurotoxicity when administered intravenously at doses up to 400 mg/kg/day. Manifestations of neurotoxicity were predominantly somnolence, fatigue and light-headedness. Less frequent manifestations were confusion, headache, dysgeusia, hypacusis, disorientation, impaired memory and exacerbation of a pre-existing neuropathy.

In the event of an overdose, discontinue the treatment and institute supportive measures.

Haemodialysis or peritoneal dialysis may be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: various alimentary tract and metabolism products, ATC code: A16A X03.

Sodium phenylbutyrate is a pro-drug and is rapidly metabolised to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine which is then excreted by the kidneys. On a molar basis, phenylacetylglutamine is comparable to urea (each containing 2 moles of nitrogen) and therefore provides an alternate vehicle for waste nitrogen excretion. Based on studies of phenylacetylglutamine excretion in patients with urea cycle disorders it is possible to estimate that, for each gram of sodium phenylbutyrate administered, between 0.12 and 0.15 g of phenylacetylglutamine nitrogen are produced. As a consequence, sodium phenylbutyrate reduces elevated plasma ammonia and glutamine levels in patients with urea cycle disorders. It is important that the diagnosis is made early and treatment is initiated immediately to improve the survival and the clinical outcome.

Previously, *neonatal-onset presentation* of urea cycle disorders was almost universally fatal within the first year of life, even when treated with peritoneal dialysis and essential amino acids or their nitrogen-free analogues. With haemodialysis, use of alternative waste nitrogen excretion pathways (sodium phenylbutyrate, sodium benzoate and sodium phenylacetate), dietary protein restriction, and, in some cases, essential amino acid supplementation, the survival rate in new-borns diagnosed after birth (but within the first month of life) increased to almost 80 % with most deaths occurring during an episode of acute hyperammonaemic encephalopathy. Patients with neonatal-onset disease had a high incidence of mental retardation.

In patients diagnosed during gestation and treated prior to any episode of hyperammonaemic encephalopathy, survival was 100 %, but even in these patients, many subsequently demonstrated cognitive impairment or other neurologic deficits.

In *late-onset deficiency* patients, including females heterozygous for ornithine transcarbamylase deficiency, who recovered from hyperammonaemic encephalopathy and were then treated chronically with dietary protein restriction and sodium phenylbutyrate, the survival rate was 98 %. The majority of the patients who were tested had an IQ in the average to low average/borderline mentally retarded range. Their cognitive performance remained relatively stable during phenylbutyrate therapy.

Reversal of pre-existing neurologic impairment is not likely to occur with treatment, and neurologic deterioration may continue in some patients.

AMMONAPS may be required life-long unless orthotopic liver transplantation is elected.

5.2 Pharmacokinetic properties

Phenylbutyrate is known to be oxidised to phenylacetate which is enzymatically conjugated with glutamine to form phenylacetylglutamine in the liver and kidney. Phenylacetate is also hydrolysed by esterases in liver and blood.

Plasma and urine concentrations of phenylbutyrate and its metabolites have been obtained from fasting normal adults who received a single dose of 5 g of sodium phenylbutyrate and from patients with urea cycle disorders, haemoglobinopathies and cirrhosis receiving single and repeated oral doses up to 20 g/day (uncontrolled studies). The disposition of phenylbutyrate and its metabolites has also been studied in cancer patients following intravenous infusion of sodium phenylbutyrate (up to 2 g/m²) or phenylacetate.

Absorption

Phenylbutyrate is rapidly absorbed under fasting conditions. After a single oral dose of 5 g of sodium phenylbutyrate, in the form of tablets, measurable plasma levels of phenylbutyrate are detected 15 minutes after dosing. The mean time to peak concentration is 1.35 hour and the mean peak concentration 218 µg/ml. The elimination half-life was estimated to be 0.8 hours. The effect of food on absorption is unknown.

Distribution

The volume of distribution of phenylbutyrate is 0.2 l/kg.

Biotransformation

After a single dose of 5 g of sodium phenylbutyrate, in the form of tablets, measurable plasma levels of phenylacetate and phenylacetylglutamine are detected 30 and 60 minutes respectively after dosing. The mean time to peak concentration is 3.74 and 3.43 hours, respectively, and the mean peak concentration is 48.5 and 68.5 µg/ml, respectively. The elimination half-life was estimated to be 1.2 and 2.4 hours, respectively.

Studies with high intravenous doses of phenylacetate showed non linear pharmacokinetics characterised by saturable metabolism to phenylacetylglutamine. Repeated dosing with phenylacetate showed evidence of an induction of clearance.

In the majority of patients with urea cycle disorders or haemoglobinopathies receiving various doses of phenylbutyrate (300 - 650 mg/kg/day up to 20 g/day) no plasma level of phenylacetate could be detected after overnight fasting. In patients with impaired hepatic function the conversion of phenylacetate to phenylacetylglutamine may be relatively slower. Three cirrhotic patients (out of 6) who received repeated oral administration of sodium phenylbutyrate (20 g/day in three doses) showed sustained plasma levels of phenylacetate on the third day that were five times higher than those achieved after the first dose.

In normal volunteers gender differences were found in the pharmacokinetic parameters of phenylbutyrate and phenylacetate (AUC and C_{max} about 30 - 50 % greater in females), but not phenylacetylglutamine. This may be due to the lipophilicity of sodium phenylbutyrate and consequent differences in volume of distribution.

Elimination

Approximately 80 - 100 % of the medicinal product is excreted by the kidneys within 24 hours as the conjugated product, phenylacetylglutamine.

5.3 Preclinical safety data

Sodium phenylbutyrate was negative in 2 mutagenicity tests, i.e. the Ames test and the micronucleus test. Results indicate that sodium phenylbutyrate did not induce any mutagenic effects in the Ames test with or without metabolic activation.

Micronucleus test results indicate that sodium phenylbutyrate was considered not to have produced any clastogenic effect in rats treated at toxic or non-toxic dose levels (examined 24 and 48 hours after a single oral administration of 878 to 2800 mg/kg). Carcinogenicity and fertility studies have not been conducted with sodium phenylbutyrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottles, with child resistant caps, containing 250 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Immedica Pharma AB
SE-113 63 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/120/001 (250 tablets)
EU/1/99/120/002 (500 tablets)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08/12/1999
Date of latest renewal: 08/12/2009

10. DATE OF REVISION OF THE TEXT

01/10/2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.