ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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/m^2/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/m^2/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/m^2/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 (≥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, 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, pancytopaenia, 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

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

1. NAME OF THE MEDICINAL PRODUCT

AMMONAPS 940 mg/g granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of granules contains 940 mg of sodium phenylbutyrate.

Excipient(s) with known effect
One small spoon of granules contains 6.5 mmol (149 mg) of sodium.
One medium sized spoon of granules contains 17.7 mmol (408 mg) of sodium.
One large spoon of granules contains 52.2 mmol (1200 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules.

The granules are off-white.

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.

AMMONAPS granules should be administered orally (to infants and children unable to swallow tablets and to patients with dysphagia) or via gastrostomy or nasogastric tube.

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 neonates, infants and children weighing less than 20 kg
- 9.9 - 13.0 g/m^2/day in children weighing more than 20 kg, adolescents and adults.

The safety and efficacy of doses in excess of 20 g/day 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/m^2/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/m^2/day.

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

The total daily dose should be divided into equal amounts and given with each meal or feeding (e.g. 4-6 times per day in small children). When taken orally, the granules are to 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).

Three dosing spoons are provided which dispense 1.2 g, 3.3 g or 9.7 g of sodium phenylbutyrate. Lightly shake the bottle before dispensing.

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

This medicinal products contain 124 mg (5.4 mmol) sodium per gram of sodium phenylbutyrate, equivalent to 6% 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.

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 (≥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, 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, pancytopaenia, 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 granules, measurable plasma levels of phenylbutyrate are detected 15 minutes after dosing. The mean time to peak concentration is 1 hour and the mean peak concentration 195 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 granules, measurable plasma levels of phenylacetate and phenylacetylglutamine are detected 30 and 60 minutes respectively after dosing. The mean time to peak concentration is 3.55 and 3.23 hours, respectively, and the mean peak concentration is 45.3 and 62.8 µg/ml, respectively. The elimination half-life was estimated to be 1.3 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

Calcium 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 25°C

6.5 Nature and contents of container

HDPE bottles, with child resistant caps, containing 266 g or 532 g of granules.

Three measuring spoons of different measures are provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

It is recommended that a heaped measuring spoon is removed from the container and a flat surface, e.g. the blade of a knife, is drawn across the top of the measure. This will give the following doses: small measure 1.2 g, medium measure 3.3 g and large measure 9.7 g of sodium phenylbutyrate.

Where a patient requires administration by tube, it is possible to re-constitute AMMONAPS in water prior to use (solubility for sodium phenylbutyrate is up to 5 g in 10 ml water). Please note that the re-constituted granules will normally produce a milky white suspension.

Where AMMONAPS granules need to be added to food, liquid or water, it is important that it is taken immediately after mixing.

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/1/99/120/003 (266 g granules)
EU/1/99/120/004 (532 g granules)

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

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 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

PATHEON France – BOURGOIN JALLIEU
40 boulevard de Champaret
BOURGOIN JALLIEU
38300
France

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

Not applicable.

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

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL FOR TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AMMONAPS 500 mg tablets
sodium phenylbutyrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg of sodium phenylbutyrate.

3. LIST OF EXCIPIENTS

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

250 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ammonaps 500 mg
[outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL FOR GRANULES

1. NAME OF THE MEDICINAL PRODUCT

AMMONAPS 940 mg/g granules.
sodium phenylbutyrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 g of granules contains 940 mg of sodium phenylbutyrate

3. LIST OF EXCIPIENTS

Contains sodium, see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

266 g granules
532 g granules
Three measuring spoons of different measures are provided.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before 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

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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/1/99/120/003 266 g granules
EU/1/99/120/004 532 g granules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Justification for not including Braille accepted]

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

B. PACKAGE LEAFLET

Package leaflet: Information for the user

AMMONAPS 500 mg tablets
Sodium 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 AMMONAPS is and what it is used for

AMMONAPS is prescribed to patients with urea cycle disorders. Patients with these rare disorders have a deficiency of certain liver enzymes and are therefore unable to eliminate nitrogen waste. Nitrogen is a building block of proteins, because of this, there is a build up of nitrogen in the body after eating protein. Nitrogen waste, in the form of ammonia, is especially toxic for the brain and leads, in severe cases, to reduced levels of consciousness and to coma.

AMMONAPS helps the body to eliminate nitrogen waste, reducing the amount of ammonia in your body.

2. What you need to know before you take AMMONAPS

Do not take AMMONAPS
- if you are pregnant.
- if you are breast-feeding.
- if you are allergic to sodium phenylbutyrate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking AMMONAPS
- if you have difficulty swallowing. AMMONAPS tablets can get stuck in the oesophagus and cause ulcers. If you have difficulty swallowing it is recommended to use AMMONAPS granules instead.
- if you suffer from heart failure, a decrease in your kidney function or other diseases, where the retention of the sodium salt contained in this medicine, may make your condition worse.
- if you have decreased kidney or liver function, since AMMONAPS is eliminated from the body through the kidney and liver.
- when given to small children, since they may not be able to swallow the tablets and may choke. It is recommended to use AMMONAPS granules instead.

AMMONAPS must be combined with a diet reduced in proteins designed especially for you by the doctor and the dietician. You must follow this diet carefully.

AMMONAPS does not completely prevent the occurrence of an acute excess of ammonia in the blood and is not appropriate for treating such a condition, which is a medical emergency.

If you require laboratory tests, it is important to remind your doctor that you are taking AMMONAPS, since sodium phenylbutyrate may influence certain laboratory test results.

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

It is especially important to tell your doctor if you are taking medicines containing:
- valproic acid (an antiepileptic drug),
- haloperidol (used in certain psychotic disorders),
- corticosteroids (cortisone-like medicines that are used to provide relief for inflamed areas of the body),
- probenecid (for treatment of hyperuricemia associated with gout).

These medicines may change the effect of AMMONAPS and you will need more frequent blood controls. If you are uncertain if your medicines contain these substances, you should check with your doctor or pharmacist.

Pregnancy and breast-feeding
Do not use AMMONAPS if you are pregnant, because this medicine can harm your unborn baby. If you are a woman who could get pregnant, you must use reliable contraception, during treatment with AMMONAPS.
Do not use AMMONAPS if you are breast-feeding, because this medicine can pass into the breast-milk and harm your baby.

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

AMMONAPS contains sodium
Each AMMONAPS tablet contains 62 mg of sodium.

Talk to your doctor or pharmacist if you need 6 or more tablets daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

3. How to take AMMONAPS

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

Dosage
The daily dose of AMMONAPS will be calculated from your protein tolerance, diet and body weight or body surface. You will need regular blood tests to determine the correct daily dose. Your doctor will tell you how many tablets you should take.

Method of administration
You should take AMMONAPS by mouth in equally divided doses with each meal (for example three times per day). You should take AMMONAPS with a large volume of water.

AMMONAPS must be taken with a special diet reduced in protein.

AMMONAPS tablets should not be given to children who are not able to swallow tablets. It is recommended that AMMONAPS granules are used instead.

You will need to have treatment and to follow a diet throughout your life, unless you have a successful liver transplantation.

If you take more AMMONAPS than you should
Patients who have taken very high doses of AMMONAPS experienced:
- sleepiness, tiredness, light-headedness and less frequently confusion,
- headache,
- changes in taste (taste disturbances),
- decrease in hearing,
- disorientation,
- impaired memory,
- worsening of existing neurological conditions.

If you experience any of these symptoms, you should immediately contact your doctor or the nearest hospital emergency department for supportive treatment.

If you forget to take AMMONAPS
You should take a dose as soon as possible with your next meal. Make sure that there are at least 3 hours between two doses. 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The frequency of possible side effects is listed below.

Very common:	Affects more than 1 user in 10
Common:	Affects 1 to 10 users in 100
Uncommon:	Affects 1 to 10 users in 1,000
Rare:	Affects 1 to 10 users in 10,000
Very rare:	Affects less than 1 user in 10,000
Not known:	Frequency cannot be estimated from the available data

Very common side effects: irregular menstrual periods and cessation of menstrual periods.
If you are sexually active and your period stops altogether, do not assume that this is caused by AMMONAPS. If this occurs, please discuss it with your doctor, because the absence of your period may be caused by pregnancy (see Pregnancy and breast-feeding section above).

Common side effects: changes in number of blood cells (red cells, white cells and platelets), reduced appetite, depression, irritability, headache, fainting, fluid retention (swelling), changes in taste (taste disturbances), pain in the abdomen, vomiting, nausea, constipation, skin odour, rash, abnormal kidney function, weight gain, altered laboratory test values.

Uncommon side effects: deficiency in red blood cells due to bone marrow depression, bruising, altered heart rhythm, rectal bleeding, stomach irritation, stomach ulcer, inflammation of the pancreas.

If persistent vomiting occurs, you should contact your doctor immediately.

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 AMMONAPS

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

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

Do not store above 30°C.

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 AMMONAPS contains

- The active substance is sodium phenylbutyrate.
  Each tablet of AMMONAPS contains 500 mg of sodium phenylbutyrate.
- The other ingredients are microcrystalline cellulose, magnesium stearate and colloidal anhydrous silica.

What AMMONAPS looks like and contents of the pack
AMMONAPS tablets are off-white, oval and embossed with "UCY 500".

The tablets are packaged in plastic bottles with child-resistant caps. Each bottle contains 250 or 500 tablets.

Marketing Authorisation Holder
Immedica Pharma AB
SE-113 63 Stockholm
Sweden

Manufacturer
PATHEON France – BOURGOIN JALLIEU
40 boulevard de Champaret
BOURGOIN JALLIEU
38300
France

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

AMMONAPS 940 mg/g granules
Sodium 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

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AMMONAPS is prescribed to patients with urea cycle disorders. Patients with these rare disorders have a deficiency of certain liver enzymes and are therefore unable to eliminate nitrogen waste. Nitrogen is a building block of proteins, because of this there is a build up of nitrogen in the body after eating protein. Nitrogen waste, in the form of ammonia, is especially toxic for the brain and leads, in severe cases, to reduced levels of consciousness and to coma.

AMMONAPS helps the body to eliminate nitrogen waste, reducing the amount of ammonia in your body.

2. What you need to know before you take AMMONAPS

Do not take AMMONAPS
- if you are pregnant.
- if you are breast-feeding.
- if you are allergic to sodium phenylbutyrate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking AMMONAPS
- if you suffer from heart failure, a decrease in your kidney function or other diseases where the retention of the sodium salt contained in this medicine may make your condition worse.
- if you have decreased kidney or liver function, since AMMONAPS is eliminated from the body through the kidney and liver.

AMMONAPS must be combined with a diet reduced in proteins, designed especially for you by the doctor and the dietician. You must follow this diet carefully.

AMMONAPS does not completely prevent the occurrence of an acute excess of ammonia in the blood and is not appropriate for treating such a condition, which is a medical emergency.

If you require laboratory tests, it is important to remind your doctor that you are taking AMMONAPS, since sodium phenylbutyrate may influence certain laboratory test results.

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

It is especially important to tell your doctor if you are taking medicines containing:
- valproic acid (an antiepileptic drug),
- haloperidol (used in certain psychotic disorders),
- corticosteroids (cortisone-like medicines that are used to provide relief for inflamed areas of the body),
- probenecid (for treatment of hyperuricemia associated with gout).

These medicines may change the effect of AMMONAPS and you will need more frequent blood controls. If you are uncertain if your medicines contain these substances, you should check with your doctor or pharmacist.

Pregnancy and breast-feeding
Do not use AMMONAPS if you are pregnant, because this medicine can harm your unborn baby. If you are a woman who could get pregnant, you must use reliable contraception, during treatment with AMMONAPS.

Do not use AMMONAPS if you are breast-feeding, because this medicine can pass into the breast-milk and harm your baby.

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

AMMONAPS contains sodium
One small white spoon of AMMONAPS granules contains 149 mg of sodium.
One medium sized yellow spoon of AMMONAPS granules contains 408 mg of sodium.
One large blue spoon of AMMONAPS granules contains 1200 mg of sodium.

Talk to your pharmacist or doctor if you need 2 or more small white spoons or 1 or more medium yellow or large blue spoons daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

3. How to take AMMONAPS

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

Dosage
The daily dose of AMMONAPS will be calculated from your protein tolerance, diet and body weight or body surface. You will need regular blood tests to determine the correct daily dose. Your doctor will tell you the amount of granules you should take.

Method of administration
You should take AMMONAPS in equally divided doses by mouth, through a gastrostomy (tube that goes through the abdomen to the stomach) or through a nasogastric tube (tube that goes through the nose to the stomach).

AMMONAPS must be taken with a special diet reduced in protein.

You should take AMMONAPS with each meal or feeding. In small children this can be 4 to 6 times per day.

To measure the dose:
- Shake the bottle lightly before opening
- Use the correct spoon to dispense the following amount of AMMONAPS: 1.2 g = small white spoon, 3.3 g = medium sized yellow spoon and 9.7 g = large blue spoon
- Take a heaped spoonful of granules out of the bottle
- Pass a flat surface, e.g. the back of a knife blade, over the top of the spoon to remove the excess of granules
- The granules left in the spoon are one spoonful
- Take the correct number of spoonfuls of granules from the bottle.

When taken by mouth
Mix the measured dose 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) and take it immediately after mixing.

Patients with a gastrostomy or nasogastric tube
Mix the granules with water until there are no dry granules left (stirring the solution helps to dissolve the granules). When the granules are dissolved in water you get a milky white liquid. Take the solution immediately after mixing.

You will need to have treatment and to follow a diet throughout your life, unless you have a successful liver transplantation.

If you take more AMMONAPS than you should
Patients who have taken very high doses of AMMONAPS experienced:
- sleepiness, tiredness, light-headedness and less frequently confusion,
- headache,
- changes in taste (taste disturbances),
- decrease in hearing,
- disorientation,
- impaired memory,
- worsening of existing neurological conditions.

If you experience any of these symptoms, you should immediately contact your doctor or the nearest hospital emergency department for supportive treatment.

If you forget to take AMMONAPS
You should take a dose as soon as possible with your next meal. Make sure that there are at least 3 hours between two doses. 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.

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Not known: Frequency cannot be estimated from the available data

Very common side effects: irregular menstrual periods and cessation of menstrual periods.
If you are sexually active and your period stops altogether, do not assume that this is caused by AMMONAPS. If this occurs, please discuss it with your doctor, because the absence of your period may be caused by pregnancy (see Pregnancy and breast-feeding section above).

Common side effects: changes in number of blood cells (red cells, white cells and platelets), reduced appetite, depression, irritability, headache, fainting, fluid retention (swelling), changes in taste (taste disturbances), pain in the abdomen, vomiting, nausea, constipation, skin odour, rash, abnormal kidney function, weight gain, altered laboratory test values.

Uncommon side effects: deficiency in red blood cells due to bone marrow depression, bruising, altered heart rhythm, rectal bleeding, stomach irritation, stomach ulcer, inflammation of the pancreas.

If persistent vomiting occurs, you should contact your doctor immediately.

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 AMMONAPS

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

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

Do not store above 25°C.

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 AMMONAPS contains

- The active substance is sodium phenylbutyrate.
  One gram of AMMONAPS granules contains 940 mg of sodium phenylbutyrate.
- The other ingredients are calcium stearate and colloidal anhydrous silica.

What AMMONAPS looks like and contents of the pack
AMMONAPS granules are off-white.

The granules are packaged in plastic bottles with child-resistant caps. Each bottle contains 266 g or 532 g of granules. Three spoons (one small white spoon, one medium sized yellow spoon and one large blue spoon) are included to measure your daily dose.

Marketing Authorisation Holder
Immedica Pharma AB
SE-113 63 Stockholm
Sweden

Manufacturer
PATHEON France – BOURGOIN JALLIEU
40 boulevard de Champaret
BOURGOIN JALLIEU
38300
France

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.