1. NAME OF THE MEDICINAL PRODUCT

GRANUPAS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 4 g of para-aminosalicylic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant granules

The granules are small off white/ light brown coloured approximately 1.5 mm diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GRANUPAS is indicated for use as part of an appropriate combination regimen for multi-drug resistant tuberculosis in adults and paediatric patients from 28 days of age and older when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults
4 g (one sachet) three times per day.
The recommended schedule is 4 g every 8 hours. GRANUPAS can be taken with food.
Maximum daily dose is 12 g. Usual duration of treatment is 24 months.

Desensitization
Desensitization can be accomplished by starting with 10 mg para-aminosalicylic acid (PAS) given as a single dose. The dosage is doubled every 2 days until reaching a total of 1 gram after which the dosage is divided to follow the regular schedule of administration. If a mild temperature rise or skin reaction develops, the increment is to be dropped back one level or the progression held for one cycle. Reactions are rare after a total dosage of 1.5 g.

Paediatric population
The optimal dose regimen in children is uncertain. Limited pharmacokinetic data suggest no substantial difference between adults and children.
For infants, children and adolescents the dosage will be adapted to the patient's weight at 150 mg/kg

per day, divided in two intakes. A dosing spoon is provided to measure small doses below 4 g for young children.

The safety and efficacy of para-aminosalicylic acid in neonates have not been established. No data are available.

Method of administration

Oral use

The contents of the sachet should be added to a glass of orange or tomato juice. They will not dissolve, but swirling the juice in the glass will help re-suspend the granules if they sink. It should be drunk at once ensuring that the granules are not left in the glass. Any granules left-over at the bottom of the glass should be swallowed immediately by adding a small quantity of liquid. Smaller doses in children should be measured using the dosing spoon and given by sprinkling on apple sauce or yogurt.

The medicinal product should be swallowed immediately after mixing with orange juice, tomato juice, apple sauce and yogurt whilst the granules are intact.

The granules should not be crushed or chewed, as this impairs the gastro-resistant coating.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe renal disease. Patients with severe renal impairment should not receive para-aminosalicylic acid. Patients with severe renal disease will accumulate the inactive acetyl metabolite of para-aminosalicylic acid.

4.4 Special warnings and precautions for use

Mild to moderate renal impairment
Given that the metabolites of para-aminosalicylic acid are largely excreted via glomerular filtration, caution is warranted in patients with mild to moderate renal impairment (see also section 4.3).

Gastric ulcer
Para-aminosalicylic acid should be used with caution in patients with peptic ulcer.

Hepatic impairment
Para-aminosalicylic acid should be used with caution in patients with hepatic impairment.

Hepatic toxicity
Para-aminosalicylic acid may cause hepatitis. The first symptoms usually appear within three months of the start of therapy with a rash as the most common adverse reaction followed by fever and much less frequently by gastrointestinal disturbances of anorexia, nausea or diarrhoea. Treatment should be stopped immediately in this case.

Hypersensitivity
The patient must be monitored carefully during the first three months of therapy and treatment must be discontinued immediately at the first sign of a rash, fever or other premonitory signs of intolerance.

See section 4.2 for posology adjustments for desensitization.

Hypothyroidism in HIV co-infected patients
Para-aminosalicylic acid may be associated with an increased risk of hypothyroidism in HIV co-infected patients. Thyroid function should be monitored in HIV co-infected patients before commencing treatment and regularly during treatment, in particular when para-aminosalicylic acid is co-administered with ethionamide/prothionamide.

Patients should be advised that the skeletons of the granules may be seen in the stools.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Results from literature suggest the following:

Vitamin B12

Vitamin B12 absorption may be reduced by para-aminosalicylic acid with clinically significant erythrocyte abnormalities developing after depletion; patients on therapy of more than one month should be considered for maintenance of vitamin B12.

Digoxin

Para-aminosalicylic acid may decrease the gastrointestinal absorption of digoxin, by inhibiting the absorption function of intestinal cells. Serum digoxin levels should be monitored in patients on concomitant therapy.

Ethionamide

Co-administration of para-aminosalicylic acid and ethionamide may intensify adverse reactions of para-aminosalicylic acid, mainly the gastrointestinal effects, including jaundice, hepatitis, nausea, vomiting, diarrhoea, abdominal pain or anorexia. Ethionamide should be withdrawn if these effects are significant.

Diphenylhydramine

This medicinal product decreases the gastrointestinal absorption of para-aminosalicylic acid, and should not be administered concomitantly.

Antiretrovirals

In a drug-drug interaction study in healthy subjects with para-aminosalicylic acid calcium (PAS-Ca) formulation, the exposure of tenofovir decreased approximately 3-fold when co-administered with multiple doses of 4000 mg PAS-Ca compared with administration of tenofovir alone. The mechanism behind this interaction is unknown. No clinical interaction data is available to determine the relevance of this interaction to the current PAS formulation, but attention should be paid to the potential risk for decreased efficacy of tenofovir when co-administered with para-amino salicylic acid.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of para-aminosalicylic acid in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3).

GRANUPAS is not recommended during pregnancy and in women of childbearing potential not using contraception.

Literature reports on para-aminosalicylic acid in pregnant women always report co-administration of other medicinal products. As there are no adequate and well controlled studies of para-aminosalicylic acid in humans, para-aminosalicylic acid should be given to a pregnant woman only if clearly needed.

Breast-feeding
Para-aminosalicylic acid is excreted in human milk. There is insufficient information on the effects of para-aminosalicylic acid in newborns/infants. GRANUPAS should not be used during breast-feeding.

Fertility
There is no evidence available on the effect of para-aminosalicylic acid on fertility.

4.7 Effects on ability to drive and use machines

Para-aminosalicylic acid must be used with caution. Para-aminosalicylic acid may affect the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Most frequent adverse reactions were related to the gastrointestinal system. Cutaneous hypersensitivity reactions were also frequent as well as adverse reactions related to the nervous system.

Tabulated list of adverse reactions

In the table below all adverse reactions are listed 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.

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, purpura, leukopenia, anemia, methemoglobinemia, agranulocytosis.
Metabolism and nutrition disorders	Rare	Hypothyroidism*.
	Very rare	Hypoglycemia.
Nervous system disorders	Very rare	Tendon pain, headache, visual abnormalities, peripheral neuropathy, dizziness.
	Common	Giddiness, vestibular syndrome.
Gastrointestinal disorders	Common	abdominal pain, vomiting, nausea, bloating, diarrhea, soft stools.
	Uncommon	Anorexia.
	Rare	Malabsorption syndrome*, peptic ulcer, gastrointestinal bleeding, jaundice, metallic taste.
Hepatobiliary disorders	Unknown	Hepatitis.
Skin and subcutaneous tissue disorders	Common	Cutaneous hypersensitivity, skin rash.
	Rare	Urticaria.
Renal and urinary disorders	Very rare	Crystalluria.
Investigations	Very rare	Decreased prothrombine level, hepatocytolysis. Increased blood alkaline phosphatase, transaminases, weight loss.

*see Description of selected adverse reactions below

Description of selected adverse reactions

Hypothyroidism
Hypothyroidism in HIV co-infected patients is a very common event and occurs in ≥1/10 subjects, particularly when para-aminosalicylic acid is administered with ethionamide/prothionamide.

Malabsorption syndrome
A malabsorption syndrome can develop in patients on para-aminosalicylic acid, but is usually not complete. The complete syndrome includes steatorrhoea, an abnormal small bowel pattern on x-ray, villus atrophy, depressed cholesterol, reduced D-xylose and iron absorption. Triglyceride absorption is always normal.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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

There is no experience with overdose in humans. In the event of overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse reactions and that appropriate symptomatic treatment is instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis.
ATC code: J04AA01

Mechanism of action

Aminosalicylic acid is bacteriostatic against *Mycobacterium tuberculosis*. It inhibits the onset of bacterial resistance to streptomycin and isoniazid.
The mechanism of action of para-aminosalicylic acid resembles the sulfonamides, competing with paraminobenzoic acid (PABA) for dihydropteroate synthetase (DHP), a key enzyme in the biosynthesis of folates. However, para-aminosalicylic acid appears to be a weak inhibitor of DHP in *vitro*, raising the possibility that it may have a different target.

5.2 Pharmacokinetic properties

Absorption

GRANUPAS is a gastro-resistant preparation and, therefore, the acid-resistant coating of the granules protects against degradation in the stomach therefore preventing the formation of meta-aminophenol (a known hepatotoxin). The small granules are designed to escape the restriction on gastric emptying of large particles. Under neutral conditions as are found in the small intestine or in neutral foods, the acid-resistant coating is dissolved within one minute.

Care must be taken in the administration of these granules to protect the acid-resistant coating by maintaining the granules in an acidic food during dosage administration.

Because the granules are protected by an enteric coating, absorption does not commence until they leave the stomach. The soft skeletons of the granules remain and may be seen in the stools.

In a single dose (4 grams) pharmacokinetic study in healthy adult volunteers (N=11) the initial time to a 2 µg/mL serum level of aminosalicylic acid was 2 hours with a range of 45 minutes to 24 hours; the median time to peak was 6 hours with a range of 1.5 to 24 hours; the mean peak level was 20 µg/mL with a range of 9 to 35 µg/mL: a level of 2 µg/mL was maintained for an average of 8 hours with a range of 5 to 9.5 a level of 1 µg/mL was maintained for an average of 8.8 hours with a range of 6 to 11.5 hours.

Distribution

Para-aminosalicylic acid is distributed in various tissues and fluids including the lungs, kidneys, liver and peritoneal fluid. Pleural or synovial fluid concentrations are approximately equal to plasma. The drug does not cross the blood brain barrier in patients unless the meninges are inflamed, when the concentration of para-aminosalicylic acid in cerebrospinal fluid is about 10 to 50% of the plasma. It is unknown whether it passes through the placental barrier. Small amounts of this agent are distributed in the milk and bile.
Plasma protein binding is about 50 to 60%, the kinetic distribution has a half-life of 0.94 hours and a

volume of distribution of 1.001 L/kg.

Biotransformation

Para-aminosalicylic acid is acetylated in the liver and converted into the inactive metabolite, N-acetyl-para-aminosalicylic acid which is devoid of bacteriostatic activity. The plasma half-life of this agent is about 1 hour, the concentration is not substantially altered in hepatic dysfunction. The concentration of the metabolite may be increased in cases of renal failure.
The major metabolites of PAS are produced by conjugation to glycine in para-aminosalicyluric acid (PASU) for up to 25% of the dose and to N-acetyl in N-acetyl para-aminosalicylic acid (Ac-PAS) for up to 70% of the dose. Together they constitute more than 90% of the total metabolites of PAS found in urine.

Elimination

In a single dose study the plasma half-life of para-aminosalicylic acid administered as GRANUPAS was 1.62±0.85 h.
Para-aminosalicylic acid and its metabolites are excreted by glomerular filtration and tubular secretion. The cumulative excretion of para-aminosalicylic after 24 hours is 84% of an oral dose of 4 g, 21% as para-aminosalicylic acid and 63% as the acetylated form. The acetylation process is not genetically determined as is the case for isoniazid.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.
The data available from a rat embryofoetal development study, where animals were given sodium aminosalicylate (3.85 to 385 mg/kg) were limited. Bone defects were observed at 77 mg/kg only, and increased foetal weight was noted at the other doses. Other malformations were observed; however, the exact nature of these findings is unknown. The lack of a dose-response relationship suggests that the findings are not of clinical relevance, but it is noted that the findings were observed at doses below those proposed clinically. In the rabbit, sodium aminosalicylate had no effects on embryofoetal development; however, the doses evaluated were below those proposed clinically.

Sodium aminosalicylic acid was not mutagenic in Ames test strain TA 100. In human lymphocyte cultures in-vitro clastogenic effects of achromatic, chromatid, isochromatic breaks or chromatid translocations were not seen at 153 or 600 µg /mL but at 1500 and 3000 µg /mL there was a dose related increase in chromatid aberrations. An *in vivo* genotoxicity study (micronucleus test) has been conducted with para-aminosalicylic acid. Results indicate that para-aminosalicylic acid was considered not to have produced any clastogenic effect in mice treated at non-toxic dose levels (examined 24 hours after 2 daily administrations of 312.5 to 1250 mg/kg).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Methacrylic acid – Ethyl acrylate Copolymer (1:1) Dispersion 30%
Talc
Dibutyl sebacate
Hypromellose
Colloidal hydrated silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
The sachets can be stored below 25°C up to 24 hours after first opening.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Sachets consisting of paper/low density polyethylene/aluminium foil/primer/low density polyethylene.

Pack size of 30 sachets. A calibrated measuring spoon is provided.

6.6 Special precautions for disposal and other handling

The sachet should not be used if it is swollen or if the granules have lost their light brown colour, and are turning dark brown or purple.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MANUFACTURER

Eurocept International BV,
Trapgans 5 1244 RL Ankeveen,
The Netherlands

8 REGISTRATION HOLDER:

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9 REGISTRATION NUMBER

160-83-34974

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