SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

P-aminosalicylate sodium (PAS sodium) delayed-release granules (60% w/w)*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains: p-aminosalicylate sodium delayed-release granules (60% w/w) 9.2 g, (equivalent to 4 grams p-aminosalicylic acid)

Each bottle contains: p-aminosalicylate sodium delayed-release granules (60% w/w) 100 g, (equivalent to 43.5 grams p-aminosalicylic acid)

Each gram of the granules contains: 6 mg sodium metabisulphite and
87 mg hydrogenated castor oil.

Each sachet contains: 55.2 mg sodium metabisulphite and
800 mg hydrogenated castor oil.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated granules
Brick red coloured enteric coated granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

P-aminosalicylate sodium delayed-release granules (60% w/w) is indicated for the treatment of tuberculosis in combination with other active agents. It is most commonly administered to patients with multi-drug resistant tuberculosis (MDR-TB) or extremely drug-resistant tuberculosis (XDR-TB) or in situations when therapy with isoniazid and rifampicin is not possible due to resistance and/or intolerance. When p-aminosalicylate sodium delayed-release granules (60% w/w) is added to the treatment regimen in patients with proven or suspected drug resistance, it should be accompanied by at least one and preferably two other new agents to which the Mycobacterium is known or expected to be susceptible.

4.2 Posology and method of administration

Oral use

Adults:
The adult dose of p-aminosalicylate sodium delayed-release granules (60% w/w) is 9.2 grams (1 sachet) twice daily.

(Note: This product is a sodium salt of PAS. The above dosing is equivalent to a dose of 4 grams of p-aminosalicylic acid twice daily.)

Children:
The dose of p-aminosalicylate sodium delayed-release granules (60% w/w) for children is 345 mg/kg/day, divided into two equal daily doses. A 2 g measuring spoon is provided with the product.

(Note: This children's dosing is equivalent to 150 mg/kg/day of p-aminosalicylic acid.)

[*] Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

In children the total dose should not exceed the adult dose, i.e. 9.2 grams of p-aminosalicylate sodium delayed-release granules (60% w/w) twice daily.

The sodium content of this product may be a potential cause for concern in children below age 1, and especially below age 6 months. Other sodium sources in the child's intake should be minimized.

Method of administration:
The granules should be suspended in a glass of water or acidic fruit juices like orange juice, stirred, and ingested immediately. The granules should not be chewed as this may cause crushing of the coating, exposing the content to acid pH in the stomach.

P-aminosalicylate sodium delayed-release granules (60% w/w) may be taken without regard to food.

The use of p-aminosalicylate sodium delayed-release granules (60% w/w) in intermittent drug regimens has not been sufficiently investigated.

Renal impairment:
P-aminosalicylate sodium delayed-release granules (60% w/w) is contraindicated in patients with severe renal disease. The sodium content of this product may be of concern even in patients with milder renal impairment. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention.

Hepatic impairment:
No dose adjustment is needed.

4.3 Contraindications

P-aminosalicylate sodium delayed-release granules (60% w/w) is contraindicated in:
- patients with hypersensitivity to the active substance or to any of the excipients
- patients with severe renal impairment

4.4 Special warnings and precautions for use

Hypersensitivity reactions: p-aminosalicylic acid may cause a hypersensitivity reaction, which commonly manifests with a skin rash and fever. This PAS sodium product is likely to do likewise. The symptoms may be accompanied by lymphadenopathy, jaundice and hepatitis, leukocytosis, conjunctivitis, headaches and joint pain. The skin rash is most commonly generalised, eyrthematous, maculopapular and pruritic. Desquamation of the skin and coarse exfoliation have been observed in extreme cases, and several deaths have been recorded. The patient must be monitored carefully, and treatment must be discontinued immediately at the first sign of a rash, fever or other premonitory signs of intolerance.

The drugs of the regimen may be restarted one at a time in very small but gradually increasing doses to determine whether the manifestations are drug-induced and, if so, which drug is responsible. Desensitisation has been accomplished successfully in 15 of 17 patients starting with 10 mg p-aminosalicylic acid given as a single dose. The dosage is doubled every two 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 of 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 grams. Other desensitization protocols have also been used, see references.

This medicinal product contains 0.6 g sodium per average adult dose (65 mg per gram of p-aminosalicylate sodium delayed-release granules (60% w/w)).
Due to the sodium load, p-aminosalicylate sodium delayed-release granules (60% w/w) should be used with caution in patients with sodium restricted diets (e.g. patients with hypertension, congestive heart failure or renal disease), and in children under 1 year old.

Liver function: In a review of 7,492 patients treated with p-aminosalicylic acid, 38 (0.5%) developed hepatitis. In 28 of these cases (0.3%), the event was attributed at least in part to p-aminosalicylic acid. Hepatitis usually appeared within three months of starting therapy. In many cases this was associated with a rash and fever (see above, hypersensitivity), and much less frequently by GI disturbances such as anorexia, nausea or diarrhoea. In 90% of these patients, premonitory symptoms preceded jaundice by a few days to several weeks. When p-aminosalicylic acid induced hepatitis was diagnosed, hepatomegaly was invariably present, with lymphadenopathy in 46%, leukocytosis in 79% and eosinophilia in 55% of cases. If liver toxicity occurs, treatment must be discontinued. According to other reported studies, failure to recognise the reaction may result in a mortality of up to 21%.

Thyroid function: p-aminosalicylic acid may cause hypothyroidism and goitre. Thyroid function should be measured at baseline and checked every three months during therapy. In a 1954 study thyroxine synthesis but not iodide uptake was reported reduced by about 40% when the sodium salt of aminosalicylic acid was administered one hour before radio-iodine.

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

Excipients:
This medicinal product contains hydrogenated castor oil, which may cause stomach upset and diarrhoea. This medicinal product also contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

P-aminosalicylic acid at a dosage of 12 grams has been reported to produce a 20% reduction in the acetylation of isoniazid, especially in rapid acetylators; INH serum levels, half lives and excretions in fast acetylators still remains half of the levels seen in slow acetylators with or without p-aminosalicylic acid. The effect is dose-related, and while it has not been studied with delayed-release preparations such as the granules, the lower serum levels with this sodium PAS preparation will likely result in a reduced effect on the acetylation of INH.

As a result of competition, vitamin B_{12} absorption has been reduced 55% by 5 grams of p-aminosalicylic acid with clinically significant erythrocyte abnormalities developing after depletion; patients on therapy of more than one month should be considered for vitamin B_{12} substitution.

4.6 Pregnancy and lactation

Some studies have suggested that higher levels of congenital defects in mothers treated with p-aminosalicylic acid. p-aminosalicylate sodium delayed-release granules (60% w/w) should only be given to a pregnant woman if the maternal condition justifies the risk to the fetus.

P-aminosalicylic acid is excreted into breast milk, and the safety of breast feeding has not been demonstrated. Breast feeding infants should be monitored for adverse effects.

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. Nevertheless, the clinical status of the patient and the adverse reaction profile of p-aminosalicylate sodium delayed - release granules (60% w/w) should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Adverse events considered at least possibly related to p-aminosalicylic acid treatment are listed below by body system, organ class and frequency. Frequency estimates are in many cases not based on adequately sized randomised trials, but on published data generated during post-approval use. Often, no frequency data can be given. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10000, <1/1000), very rare (<1/10000), 'not known'.

Nervous system disorders:
Not known: optic neuritis, encephalopathy

Gastrointestinal disorders:
Common: nausea, vomiting, abdominal pain
Not known: diarrhoea

Hepatobiliary disorders:
Uncommon: jaundice, hepatitis

Metabolism and nutrition disorders
Not known: hypothyroidism, goitre, hypoglycemia, malabsorption syndrome

Renal and urinary disorders
Not known: hypokalemia

Skin and subcutaneous tissue disorders:
Not known: rash, exfoliative dermatitis

General disorders
Not known: Fever

Blood and lymphatic systems disorders:
Not known: leucopenia, agranulocytosis, thrombocytopenia, eosinophilia. Coombs positive haemolytic anemia, reduction in prothrombin

Vascular disorders:
Not known: vasculitis

Respiratory, thoracic and mediastinal disorders:
Not known: Eosinophilic pneumonia

4.9 Overdose

Overdosage has not been reported. There is no antidote. Supportive treatment may be warranted.

P-aminosalicylic acid is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial
ATC Code J04AA02

Mechanism of action
p-aminosalicylic acid inhibits the onset of bacterial resistance to streptomycin and isoniazid. The mechanism of action has been postulated to be inhibition of folic acid synthesis (but without potentiation with antifolic compounds) and/or inhibition of synthesis of the cell wall component, mycobactin, thus reducing iron uptake by *M. tuberculosis*.

5.2 Pharmacokinetic properties

Following single dose administration of 11 g of p-aminosalicylate sodium delayed-release granules (60% w/w) (equivalent to 4.78g of p-aminosalicylic acid) administration in healthy volunteers, the mean (CV) p-aminosalicylic acid Cmax value was 21.4 μg/ml (51 %), respectively and the corresponding value for AUC(0-inf) was 121 μg*h/ml (44 %). The apparent t1/2 was 1.94h. The mean plasma concentration after 12 hours was 4.36 μg/ml, which is above the MIC of 1 μg/ml for M. Tuberculosis.

Approximately 50-60% of p-aminosalicylic acid is protein bound. Penetration into the cerebrospinal fluid occurs only if the meninges are inflamed.

80% of p-aminosalicylic acid is excreted in the urine, with 50% or more of the dosage excreted in acetylated form. The acetylation process is not genetically determined, unlike isoniazid. P-aminosalicylic acid is excreted by glomerular filtration; although previously reported otherwise, probenecid, a tubular blocking agent, does not decrease elimination.

Special populations

Renal impairment

Patients with severe renal disease will accumulate p-aminosalicylic acid and its acetyl metabolite but will continue to form the inactive, acetylated metabolite. The half-life of free p-aminosalicylic acid in renal disease is approximately similar in renal disease and healthy volunteers, but the half-life of the inactive, acetylated metabolite is prolonged sixfold in patients with uremia. Although p-aminosalicylic acid is dialyzable, the frequency of chronic hemodialysis is usually not sufficient to compensate for the reduced elimination due to renal failure.

Hepatic impairment:

The metabolism of p-aminosalicylic acid has been reported to be comparable to that in normal volunteers.

Children and adolescents:

Pharmacokinetic documentation in children and adolescents is lacking

5.3 Preclinical safety data

Sodium aminosalicylate produced an occipital bone defect, probably with a dose response, when administered to ten pregnant Wistar rats at five doses from 3.85 to 385 mg/kg from days 6 to 14. There were no significant changes from controls in any group in corpora lutea, early resorptions, total resorptions, fetal death, litter size, or hematomas. For all except the 77 mg/kg group, fetal weights were significantly greater than controls. Chinchilla rabbits on 5 mg/kg from days 7 to 14 did not show any significant differences as compared to controls for the same parameters studied.

Sodium aminosalicylic acid was not mutagenic in Ames tester 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. At 1500 and 3000 µg/mL there was a dose related increase in chromatid aberrations.

Patients on isoniazid and aminosalicylic acid have been reported to have an increased number of chromosomal aberrations as compared to controls.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite, microcrystalline cellulose, crospovidone, hydrogenated vegetable oil, hydrogenated castor oil, butylated hydroxyl toluene, ethyl cellulose, stearic acid, dibutyl phthalate, methacrylic acid-methyl methacrylate copolymer, purified talc, titanium dioxide, colour iron oxide red and colour quinoline yellow supra.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months in original pack.

30 days after first opening of the primary pack in case of HDPE container

6.4 Special precautions for storage

Do not Store above 25^{o}C. Store in dry place, protected from light.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

100g granules packed in a triple laminated Alu/PET/Alu/LLDPE sachet. The sachet is further packed in a HDPE bottle along with a blue colour "4.6g measuring spoon (0.5g, 1.0g, 1.5g, 2.0g, 2.5g, 3.0g, 3.5g, 4.0g and 4.6g marking) & tagger sealed" -Overflow Capacity–610 ml–650 ml.

100 g granules packed in LDPE bag and placed in a triple laminated Alu/PET/Alu/LLDPE sachet. The sachet is further packed in a HDPE bottle along with a blue colour "4.6 g measuring spoon (0.5g, 1.0g, 1.5g, 2.0g, 2.5g, 3.0g, 3.5g, 4.0g and 4.6g marking) and tagger sealed" – Overflow Capacity – 610 ml – 650 ml.

9.2g granules packed in a triple laminated (Alu/PET/Alu/LLDPE) sachet, such 30 sachets are contained in a box with the leaflet. The sachets are packed along with a blue colour "4.6g measuring spoon (0.5g, 1.0g, 1.5g, 2.0g, 2.5g, 3.0g, 3.5g, 4.0g and 4.6g marking).

6.6 Special precautions for disposal

No special requirements.
Any unused product or empty container should be disposed of in accordance with local requirements.

7. SUPPLIER

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9. DATE OF FIRST PREQUALIFICATION/ LAST RENEWAL

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10. DATE OF REVISION OF THE TEXT

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Sections 2 and 6 updated in February 2019

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