SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

p-Aminosalicylate sodium 5.52 g powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance
Sodium aminosalicylate dihydrate (*Natrii aminosalicylas dihydricus*).
Each sachet contains 5.52 g of sodium aminosalicylate dihydrate, which is equivalent to 4.00 g of aminosalicylic acid.

Excipient(s) with known effect
Each sachet contains 6.94 g of lactose monohydrate.
Each sachet contains 0.04 g of aspartame (E951).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.
Almost white to cream colour powder. Colour heterogeneity is acceptable.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of tuberculosis of various forms and localisations in combination with other medicines.

4.2 Posology and method of administration

Posology

p-Aminosalicylate sodium is used only in combined treatment regimens with other medicines for the treatment of tuberculosis.

Adults
The dose is 8-12 g daily. The daily dose should be divided into 2-3 single doses.
In cachectic patients (body weight less than 50 kg) and patients with poor drug tolerability, the dose should be reduced to 4-8 g daily.
The maximum dose is 12 g daily.

Patients with renal failure
In patients with renal failure (creatinine clearance <30 ml/min), the dose is 8 g daily divided into 2 single doses.

Patients with hepatic failure
There are no data indicating the need for dose reduction; however, liver function should be monitored during the treatment.

Elderly patients
There is no information regarding use of p-Aminosalicylate sodium in elderly patients.

Paediatric population
In children, the dose is 200-300 mg/kg of body weight daily divided into 2-4 single doses. There is no information that safety of this medicine use is restricted in children of any particular age group.

Method of administration

The medicine should be taken orally after meals, in order to diminish the irritating effect on gastric mucosa. The content of the sachet should be dissolved by stirring in 100 ml of boiled water; the prepared solution should be consumed immediately.

4.3 Contraindications

- Hypersensitivity to aminosalicylic acid, its salts or to any of the excipients listed in section 6.1.
- Severe hepatic failure, hepatitis, hepatic cirrhosis.
- Severe renal failure.
- Severe heart failure.
- Gastric and duodenal ulcer.
- Myxoedema.
- Amyloidosis.
- Pregnancy and breast-feeding.

p-Aminosalicylate sodium 5.52 g powder for oral solution contains the sweetener aspartame. Its administration is contraindicated in patients with phenylketonuria.

4.4 Special warnings and precautions for use

Particular caution should be exercised in patients with gastric and/or intestinal diseases, hepatic and renal impairment, or cardiac failure (in case of severe disorders, administration is contraindicated).

Prolonged use of the medicine at high doses may cause an impairment of thyroid gland function. It should be taken into account in tuberculosis patients with hypofunction of the thyroid gland.

By using p-Aminosalicylate sodium, crystalluria may develop. Its development is prevented by maintaining the urine at neutral or alkaline pH.

Patients with glucose-6-phosphate dehydrogenase deficiency should use the medicine with caution due to the risk of haemolytic anaemia.

Patients who are advised to restrict their dietary sodium ion intake, are not recommended to take p-Aminosalicylate sodium.

Blood and urine parameters, as well as liver function characteristics, should be monitored periodically.

Hypothyroidism in HIV co-infected patients
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, especially if aminosalicylic acid is administered concomitantly with ethionamide/protionamide.

Aspartame. Each sachet of p-Aminosalicylate sodium 5.52 g powder for oral solution contains 0.04 g of the sweetener aspartame. Aspartame is a source of phenylalanine. It may be harmful for patients with phenylketonuria.

Lactose. Each sachet of p-Aminosalicylate sodium 5.52 g powder for oral solution contains 6.94 g of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Several drugs with different mechanisms of action against tuberculosis mycobacteria are used concomitantly in tuberculosis therapy. Combined therapy delays onset of the development of mycobacterial resistance, and mutually enhances the effect of each drug.

p-Aminosalicylate sodium therapy delays the development of tuberculosis mycobacteria resistance to isoniazid and streptomycin. Combination with isoniazid may cause the risk of haemolytic anaemia.

The efficacy of p-Aminosalicylate sodium decreases when taking p-Aminosalicylate sodium in combination with aminobenzoates. When p-Aminosalicylate sodium is taken concomitantly with anticoagulants, anticoagulant activity increases because p-Aminosalicylate sodium also inhibits prothrombin synthesis in the liver.

Probenecid (uricosuric agent) inhibits excretion of the drug in the urine resulting in increased p-Aminosalicylate sodium plasma concentration and toxicity risk (the dose should be reduced).

p-Aminosalicylate sodium may cause vitamin B12 absorption disorders and avitaminosis. In these cases, parenteral form of vitamin B12 is recommended for administration.

Patients must not consume alcohol or smoke during the treatment.

4.6 Fertility, pregnancy and lactation

Use is contraindicated.
p-Aminosalicylate sodium, like other sulphanilamides, affects synthesis of RNA, DNA and proteins, and can also influence the function of the foetal thyroid gland. Administration of this medicine during the first three months of pregnancy can cause foetal malformations.
p-Aminosalicylate sodium is excreted in low concentration into breast milk. The medicine must not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

If there is no inflammation of the meninges, the medicine has no influence on the ability to drive and use machines, because an insignificant quantity of the active substance crosses the blood-brain barrier.

4.8 Undesirable effects

The frequency of adverse effects is defined as follows: very common (≥1/10); common (≥1/100 up to <1/10); uncommon (≥1/1,000 up to <1/100); rare (≥1/10,000 up to < 1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: leukopenia, haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase deficiency).

Immune system disorders
Rare: hypersensitivity reactions (fever, bronchospasm, eosinophilia).

Endocrine system disorders
Hypothyroidism may occur with prolonged administration of high doses.

Metabolism and nutrition disorders
Rare: hypothyroidism*.
Not known: decreased appetite, loss or lack of appetite, anorexia.

Vascular disorders
Rare: vasculitis.

Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea, abdominal pain.
Not known: upper abdominal pain (epigastric pain, gastric pain), abdominal discomfort, gastric discomfort, heaviness in stomach, abnormal faeces, dyspepsia or exacerbation of existing symptoms, heartburn, flatulence and related conditions.
In case of adverse effects, the dose should be reduced, or the medicine use should be discontinued temporarily. The adverse effects are less pronounced, if the patient follows a regular eating regimen of three meals per day.

Hepatobiliary disorders
Rare: jaundice, hepatitis.

Skin and subcutaneous tissue disorders
Rare: skin rash.
Not known: pruritus.

Musculoskeletal and connective tissue disorders
Rare: joint pain.

Renal and urinary disorders
Rare: crystalluria.

General disorders and administration site conditions
Not known: weakness, including general weakness, asthenia.

* Description of selected adverse reactions
Hypothyroidism in HIV co-infected patients is very common, and occurs in ≥1/10 subjects, especially when aminosalicylic acid is administered concomitantly with ethionamide/protionamide.

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 State Agency of Medicines, 15 Jersikas Street, Riga, LV 1003.
Website: www.zva.gov.lv

4.9 Overdose

Symptoms: nausea, vomiting, diarrhoea, psychosis may develop.
Measures: to delay absorption, activated charcoal is indicated; stomach lavage should be performed, and vital signs monitored. Treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimycobacterials, drugs for treatment of tuberculosis, aminosalicylic acid and derivatives,
ATC code: J04AA02

p-Aminosalicylate sodium 5.52 g powder for oral solution is a second-line antituberculotic drug with bacteriostatic activity against tuberculosis mycobacteria *Mycobacterium tuberculosis*. Bacteriostatic activity of the drug is based on the competition of aminosalicylic acid with its structural analogue, aminobenzoic acid, in the synthesis of folic acid, which is necessary for the process of growth and multiplication of tuberculosis mycobacteria. Aminosalicylic acid replaces aminobenzoic acid in the synthesis of folic acid, and, as a result, normal synthesis of RNA, DNA and proteins of tuberculosis mycobacteria is inhibited. In order to compete with aminobenzoic acid, high doses of p-Aminosalicylate sodium are necessary. p-Aminosalicylate sodium does not have any effect on other microorganisms. p-Aminosalicylate sodium activity

against tuberculosis mycobacteria is lower compared to first-line medications; therefore, p-Aminosalicylate sodium is combined with other, more efficient antituberculotics. In monotherapy, tuberculosis mycobacteria rapidly develop resistance to p-Aminosalicylate sodium. In combination therapy, mycobacterial drug resistance develops more slowly.

5.2 Pharmacokinetic properties

Absorption and distribution
p-Aminosalicylate sodium is well absorbed from the gastrointestinal tract after oral administration. p-Aminosalicylate sodium is better absorbed than aminosalicylic acid. Following an oral dose administration of p-Aminosalicylate sodium, equivalent to 4 g of aminosalicylic acid, peak plasma concentration, of approximately 75 μg/ml, is reached within 0.5-1 hour. Only 15 % of administered dose binds to plasma proteins. The active substance rapidly distributes in all tissues and fluids of the body, including peritoneal, pleural and synovial fluids, where its concentration is not significantly different from plasma concentration. Low concentration is in cerebrospinal fluid, where an increase in concentration of the active substance is possible only in case of meningeal inflammation. p-Aminosalicylate sodium crosses the placental barrier and is excreted into breast milk.

Biotransformation and elimination
Approximately 50 % of the active substance is metabolised in the liver by acetylation, forming inactive metabolites. The elimination half-life is one hour. In case of renal disorders, the elimination half-life may increase up to 23 hours. 85 % of the dose is excreted in the urine within 7-10 hours by glomerular filtration and tubular secretion. 14-33 % of the dose is excreted in the urine unchanged, and 50 % as metabolites.

5.3 Preclinical safety data

Repeated dose toxicity. In studies on rats, that daily received a dose of 1,000 mg/kg of aminosalicylic acid with food for 2-3 months, reversible growth disorders caused by thyroid gland hyperplasia were detected. This result was also confirmed by data from other studies.

Data from non-clinical standard studies do not indicate *mutagenicity or carcinogenicity* of aminosalicylic acid.

Embryotoxicity and teratogenicity. When pregnant female rats received p-Aminosalicylate sodium at doses of 3.85 mg/kg to 385 mg/kg during the first 6-14 days of pregnancy, occipital bone deformities were observed in the offspring. Based on data of this study, p-Aminosalicylate sodium is contraindicated during pregnancy, although similar deformities were not observed in another study in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Aspartame (E951)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
Do not store above 30 °C.

6.5 Nature and contents of container

For hospital use.
Sachet of laminated material (paper/polyethylene film/aluminium foil/polyethylene film), which contains 5.52 g of sodium aminosalicylate dihydrate. Total powder mass is 12.5 g.
25 or 300 sachets of laminated material together with the package leaflet in a cardboard box.

Sachet of laminated material (paper/polyethylene film/aluminium foil/ethylene and acrylic acid copolymer film), which contains 5.52 g of sodium aminosalicylate dihydrate. Total powder mass is 12.5 g.
25 or 300 sachets of laminated material together with the package leaflet in the cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

00-0167

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th of March, 2000
Date of latest renewal: 18th of June, 2010

10. DATE OF REVISION OF THE TEXT

05/2019