1. NAME OF THE MEDICINAL PRODUCT

p-Aminosalicylate sodium 5.52 g powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION OF THE PRODUCT

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

Excipients
Each sachet of powder contains 6.94 g of lactose monohydrate.
Each sachet of powder contains 0.04 g aspartam (E951).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.
Powder of almost white to cream colour. Nonuniformity of colour is allowed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of tuberculosis in combination with other antituberculotics.

4.2 Posology and method of administration

PAS-Na powder is used only in combined chemotherapy regiments with other medicines for the treatment of tuberculosis.

The medicine should be taken after meals in order to diminish an irritating effect on stomach mucosa. Before administration the content of a sachet is dissolved by mixing in 100 ml of water and the prepared solution should be used immediately.

Adults are administered 8-12 g/day, divided into 2-3 daily doses. The daily dose should be decreased to 4-8 g/day for cachectic patients (with body weight less than 50 kg), and for those patients who have difficulty tolerating the preparation.

Children are administered 200-300 mg/kg body weight/day, divided into 2-4 doses. There is no information that safe use of this medicine is restricted to children of any particular age group. Maximum dose is 12 g a day.

Patients with renal insufficiency (creatinine clearance <30 ml/min) - the dose is 8 g/day, divided into 2 doses.

Patients with hepatic insufficiency - there are no data regarding the need for dose reduction, however liver function tests should be monitored periodically during the treatment period.

There is no information regarding PAS-Na powder use in *elderly patients.*

4.3 Contraindications

- Hypersensitivity to PAS-Na salt and/or any of the excipients;
- severe liver insufficiency, hepatitis, cirrhosis of the liver;
- severe kidney insufficiency;
- severe heart failure;
- stomach ulcer and duodenal ulcer;
- myxoedema;

- amyloidosis;
- pregnancy or breastfeeding.

The product *p-Aminosalicylate sodium 5.52 g powder for oral solution* contains the sweetener aspartame. Its administration is contraindicated in patients who have phenylketonurea.

4.4 Special warnings and special precautions for use

Administer with caution in patients who have gastrointestinal diseases, liver and/or kidney disorders, or cardiac failure (in case of severe cases of these disorders, administration is contraindicated).

It should be taken into account that prolonged usage of the preparation at high doses may cause decrease of thyroid gland function in tuberculosis patients with hypofunctioning of the thyroid gland.

When PAS-Na is used, crystalluria may develop. Maintaining the urine at neutral or alkaline pH may help prevent development of crystals in the urine.

Patients with glucose-6-phosphate dehydrogenase deficiency should use the preparation with caution as haemolytic anaemia may develop.

Patients, who have a restricted sodium intake are not recommended to take PAS-Na.

Bood and urine parameters as well as liver function should be monitored.

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 and can be harmful for patients with phenylketonurea.

Lactose. Each sachet of *p-Aminosalicylate sodium 5.52 g powder for oral solution* contains 6.94 g of lactose monohydrate. This medicine should not be used in patients with rare inherited galactose intolerability, *Lapp* lactase deficiency or glucose-galactose malabsorbtion.

4.5 Interaction with other medicinal products and other forms of interaction

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

PAS-Na therapy delays the development of tuberculosis mycobacteria resistance to izoniazid and streptomycin. Combination with izoniazid may increase the risk of hemolytic anaemia.

Taking PAS-Na in combination with aminobenzoates decreases the efficacy of PAS-Na. When PAS-Na is taken in combination with anticoagulants the effect of anticoagulants is increased because PAS-Na also causes depression of prothrombin synthesis in the liver.

Probenicid (uricosurics) inhibits excretion of the drug in the urine which can cause increased PAS-Na toxicity risk, therefore the dose of PAS-Na should be decreased during coadministration.

PAS-sodium salt may cause reduction of vitamin B_{12} absorption and avitaminosis. In these cases it is recommended to administer vitamin B_{12} in parenteral form..

Patients should not use alcohol or smoke during therapy.

4.6 Pregnancy and lactation

Use is contraindicated during pregnancy and lactation.
PAS-Na as well as other sulphanilamides may affect synthesis of RNA, DNA and proteins, and can also influence the function of the foetal thyroid gland. Administration in the first three months of pregnancy can cause malformation of the foetus.

PAS-sodium salt is excreted in breast milk in low concentrations. The medicine is contraindicated during breastfeeding.

4.7 Effects on ability to drive and use machines

If there is no inflammation of the meninges, the preparation has no effect 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

Side effects frequency classification:
Very common – (≥ 1/10), common – (≥ 1/100 till < 1/10); uncommon - (≥ 1/1000 till < 1/100); rare (≥ 1/10 000 till < 1/1000); very rare (< 1/10 000), no information (impossible to determine from available data).

Blood and lymphatic system disorders: rare - leucopenia, haemolytic anaemia, (patients with glucose-6-phosphate dehydrogenase deficiency).
Immune system disorders: rare – hypersensitivity (fever, urticaria, bronchospasm, eosinophilia).
Endocrine system disorders: prolonged administration of high doses may cause hypothyroidism.
Cardiovascular system disorders: rare - vasculitis.
Gastrointestinal tract disorders: common - nausea, vomiting, diarrhea, abdominal pain. As soon as these adverse effects appear, the dose should be decreased, or the preparation should be discontinued for a short time. The adverse effects may be minimized if the patient follows a regular regime of three meals per day.
Liver and/or biliary tract system disorders: rare - jaundice, hepatitis.
Musculoskeletal and connective tissue disorders: rare - joint pain.
Renal and urinary disorders: crystalluria.

4.9 Overdose

Symptoms: dizziness, vomiting, diarrhea, psychosis may develop.

Procedures: to delay absorption activated charcoal is indicated, stomach lavage should be performed, and vital signs monitored. Provide symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antituberculotics, aminosalicylic acid and its derivatives.

ATC code: J04A A02.

p-Aminosalicylate sodium 5.52 g powder for oral solution is a second-line, synthetic antituberculotic with bacteriostatic activity against *Mycobacterium tuberculosis*. The basis of the bacteriostatic activity of the preparation is competition of PAS with its structural analogue, para-aminobenzoic acid (PABA), in the synthesis of folic acid, which is necessary for the process of growth and multiplication of *Mycobacterium tuberculosis.* PAS replaces PABA in the synthesis of folic acid and, as a result, normal synthesis of RNA, DNA and proteins of *Mycobacterium tuberculosis* is inhibited. In order to compete with PABA, high doses of PAS- sodium salt are necessary. PAS does not have any effect on other microorganisms. PAS-sodium salt antituberculotic activity is lower than first-line preparations, therefore PAS-sodium salt is combined with other, more effective antituberculotics. During monotherapy with the preparation, *Mycobacterium tuberculosis*

rapidly develops resistance to PAS, however with combined therapy development of drug resistance is slower.

5.2 Pharmacokinetic properties

PAS-sodium salt is rapidly absorbed from the gastrointestinal tract after oral administration. The sodium salt is absorbed more rapidly than aminosalicylic acid. After oral intake of a dose equivalent to 4 g of aminosalicylic acid, peak plasma concentration is attained within 0.5-1 hour. Only 15% of an oral dose binds to plasma proteins. The active substance rapidly penetrates into all tissues and fluids, including peritoneal, pleural and synoviomal fluids, where its concentration is not significantly different from plasma concentration. Low concentrations occur in cerebrospinal liquid, and significant levels are seen only in the case of meningeal inflammation. PAS crosses the placenta and is excreted with breast milk.
About 50% of the active substance is metabolised in the liver by acetylation into inactive metabolites. The elimination half-life is one hour. In cases of renal insufficiency the elimination half-life may increase to 23 hours. Roughly 85% of the administered dose is excreted in the urine over 7-10 hours through glomerular filtration and tubular secretion. Approximately 14-33% of the administered dose is excreted in the urine unchanged and 50% as metabolites.

5.3. Preclinical safety data

Repeated dose toxicity. In studies on rats, which received 1000 mg/kg/d of aminosalicylic acid with food for 2-3 months, recurring growth disorders caused by thyroid gland hyperplasia were observed. This result was confirmed by data from other studies.

Mutagenicity and cancerogenicity. The data from standard nonclinical studies did not show evidence of PAS-Na mutagenicity or carcinogenicity.

Embryotoxicity and teratogenicity. When pregnant female rats were administered PAS-Na salt at doses of 3.85 mg/kg to 385 mg/kg on days 6-14 of pregnancy, bone deformities were observed in the rat progeny. Although similar deformations were not seen in rabbit studies, in light of these findings PAS-Na salt is contraindicated during pregnancy,

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 below 25 °C. Protect from light and humidity.

6.5 Nature and contents of container

Sachet of laminated material (paper/polyethylene/aluminium foil/polyethylene), which contains 5.52 g of aminosalicylic acid sodium dihydrate. Total powder mass in each sachet is 12.5 g.
25 sachets and package leaflet in the carton pack or 300 sachets in the carton box.
All package sizes may not be available on the market.

6.6 Instructions for use and handling

No special requirements.
Any unused 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

00-0167

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15.03. 2000: PAS-Na powder
13.05. 2005: PAS-Na powder for oral solution
18.06. 2010: PAS-Na Olainfarm 5.52 g powder for oral solutions

10. DATE OF REVISION OF THE TEXT

06.2010