## PROFESSIONAL INFORMATION

### SCHEDULING STATUS

S4

APPROVED
PV Officer / RA Pharmacist
Sign: ..... Date: 17 Sept. 2019

### PROPRIETARY NAME AND DOSAGE FORM

PASER GRANULES delayed-release granules

### COMPOSITION

Each packet contains 4 g of p-aminosalicylic acid.

The excipients are colloidal silicon dioxide, dibutyl sebacate, Eudragit L-30D, hydroxypropyl methylcellulose, microcrystalline cellulose, and talc.

PASER GRANULES is sugar free.

### PHARMACOLOGICAL CLASSIFICATION

A 20.2.3 Tuberculostatics

### PHARMACOLOGICAL ACTION

**Pharmacodynamic properties:**

p-Aminosalicylic acid is bacteriostatic against Mycobacterium tuberculosis. 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.

**Pharmacokinetic properties:**

After two hours in simulated gastric fluid, 10 % of unprotected p-aminosalicylic acid is decarboxylated to form meta-aminophenol, a known hepatotoxin. The p-aminosalicylic acid granules in PASER GRANULES are a delayed-release granule preparation, formulated to protect against degradation in the stomach.

Under neutral conditions *in vitro*, and as are found in the small intestine or in neutral foods such water and milk, the acid-resistant coating is dissolved within one minute.

**Absorption and excretion:**

In a single 4 gram pharmacokinetic study with food in normal volunteers the initial time to a 2 µg/ml serum level of p-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 7,9 hours with a range of 5 to 9; a level of 1 µg/ml was maintained for an average of 8,8 hours with a range of 6 to 11,5 hours. The recommended schedule is 4 grams every 8 hours.

80 % of p-aminosalicylic acid is excreted in the urine, with 50 % or more of the dosage excreted in acetylated form. p-Aminosalicylic acid is excreted by glomerular filtration. The half-life of p-aminosalicylic acid is about 1 hour.

Penetration into the cerebrospinal fluid occurs only if the meninges are inflamed.

Approximately 50-60 % of p-aminosalicylic acid is protein bound; binding is reported to be reduced 50 % in kwashiorkor.

***Microbiology:***

The p-aminosalicylic acid MIC for M. tuberculosis in 7H11 agar was less than 1,0 µg/ml for nine strains including three multidrug resistant strains, but 4 and 8 µg/ml for two other multidrug resistant strains.
The 90 % inhibition in 7H12 broth (Bactec) showed little dose response but was interpreted as being less than or equal to 0,12 to 0,25 µg/ml for eight strains of which three were multi-resistant, 0,50 µg/ml for one resistant strain, questionable for four non-resistant strains and greater than 1 µg/ml for one non-resistant and three resistant strains.

p-Aminosalicylic acid is not active *in vitro* against M. avium

## INDICATIONS

PASER GRANULES is indicated in combination with other active anti-tuberculosis agents in patients with Multi-Drug Resistant TB (MDR-TB) or in situations when therapy with isoniazid and rifampicin is not possible due to a combination of resistance and/or intolerance.

When PASER GRANULES 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 agents to which the patient's organism is known or expected to be susceptible.

## CONTRAINDICATIONS

Hypersensitivity to any of the ingredients, including the excipients of PASER GRANULES.

Severe renal disease (see WARNINGS AND SPECIAL PRECAUTIONS).

Severe hepatic disease (see WARNINGS AND SPECIAL PRECAUTIONS).

## WARNINGS AND SPECIAL PRECAUTIONS

General:

PASER GRANULES should be used with care in patients with:

- renal impairment
- gastric ulcer
- G6PD deficiency.

Severe renal disease:

Patients with severe renal disease will accumulate p-aminosalicylic acid as in PASER GRANULES and its acetyl metabolite, but will continue to acetylate, thus leading exclusively to the inactive acetylated form; deacetylation, if any, is not significant.

The half-life of free p-aminosalicylic acid as in PASER GRANULES in renal disease is 30,8 minutes in comparison to 26,4 minutes in normal volunteers, but the half-life of the inactive metabolite is 309 minutes in uraemic patients in comparison to 51 minutes in normal volunteers. Although p-aminosalicylic acid as in

PASER GRANULES passes dialysis membranes, the frequency of dialysis usually is not comparable to the half-life of 50 minutes for the free acid. Patients with severe renal disease should not receive PASER GRANULES (see CONTRAINDICATIONS).

G6PD deficiency:

Case reports suggest a possible association between PASER GRANULES and haemolytic anaemia in G6PD deficiency when the medicinal product is administered intravenously and/or at higher doses than are recommended for PASER GRANULES oral formulation. Cross-transfusion studies do not support an association between oral p-aminosalicylic acid as in PASER GRANULES at a dose of 10 grams per day and haemolysis in the variants of G6PD deficiency tested (Canton and B(-)Chinese).

Liver impairment:

Severe hepatic disease is a relative contraindication. PASER GRANULES should be given with care to patients with hepatic impairment. The possibility of hepatic tuberculosis should be considered when weighing the risk-benefit ratio of including PASER GRANULES in the treatment regimen.

PASER GRANULES may cause hepatitis. The first symptom usually appears within three months of the start of therapy with a rash as the most common event followed by fever and much less frequently by gastrointestinal disturbances of anorexia, nausea or diarrhoea.

Premonitory symptoms may precede jaundice by a few days to several weeks, with half of the adverse reactions occurring during the third, fourth or fifth weeks. If recognised in the premonitory stage, the reaction is reported to "settle" in 24 hours and no jaundice ensues. Failure to recognise the reaction can result in a mortality of up to 21 %. The patient must be monitored carefully during the first three months of therapy. Treatment should be discontinued immediately at the first sign of a rash, fever or other premonitory signs of intolerance.

No studies of PASER GRANULES re-challenge have been reported. In the case of confirmed moderate or severe medicine-induced hepatotoxicity, treatment should be stopped.

Hypersensitivity:

All medicines should be stopped at the first sign suggesting a hypersensitivity reaction. Some medicines may be restarted one at a time in very small but gradually increasing doses to determine whether the hypersensitivity manifestations are medicine-induced and, if so, which medicine is responsible. This formulation is not suitable for desensitisation purposes.

Other:

Care must be taken in the administration of PASER GRANULES to protect the acid-resistant coating by maintaining the granules in an acidic food, such as yoghurt, apple sauce and orange juice during dosage administration.

Because the granules are protected by an enteric coating, the soft skeletons of the granules remain and may be seen in the stool.

**Effects on ability to drive and use machines**

PASER GRANULES has not been studied for ability to drive and use machines. However, neuropsychiatric side effects that could affect driving may occur.

**INTERACTIONS**

PASER GRANULES may produce a reduction in the acetylation of isoniazid, especially in patients who are rapid acetylators. The effect is dose related.

Vitamin $B_{12}$ absorption may be reduced by PASER GRANULES with clinically significant erythrocyte abnormalities or megaloblastic anaemia developing after depletion. Patients treated with PASER GRANULES should be considered for prophylactic therapy with $B_{12}$ maintenance.

A malabsorption syndrome may develop in patients on PASER GRANULES. The complete syndrome includes steatorrhoea, an abnormal small bowel pattern on X-ray, villus atrophy, depressed cholesterol, reduced D-xylose, iron Vitamin $B_{12}$ and folate absorption.

PASER GRANULES 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 PASER GRANULES and ethionamide may intensify adverse reactions of PASER GRANULES, mainly the gastrointestinal and hepatic side effects, including jaundice, hepatitis, nausea, vomiting, diarrhoea, abdominal pain or anorexia. Ethionamide should be withdrawn if these effects are significant.

*Diphenylhydramine*

Diphenylhydramine decreases the gastrointestinal absorption of PASER GRANULES, and should not be administered concomitantly.

Laboratory tests:

PASER GRANULES has been reported to interfere technically with the serum determinations of albumin by dye-binding, AST and ALT by the azoene dye method and with qualitative urine tests for ketones, bilirubin, urobilinogen or porphobilinogen using Ehrlich's reagent. PASER GRANULES may interfere with tests for glucosuria using copper reagents.

**HUMAN REPRODUCTION:**

Safety and efficacy has not been established in pregnancy and lactation.

Because there are no adequate and well controlled studies in humans, PASER GRANULES should not be given to a pregnant woman.

The active ingredient in PASER GRANULES is distributed into breast milk.

Mothers on PASER GRANULES should not breastfeed their infants.

## DOSAGE AND DIRECTIONS FOR USE

PASER GRANULES should be administered in combination with other medicines to which the organism is known or expected to be susceptible. The granules should be given by sprinkling on apple sauce or yoghurt or by swirling the glass to suspend the granules in an acidic drink such as tomato or orange juice.

*Adults:*

4 grams (one packet) three times per day.

*Infant, children and adolescents*:

For infants, children and adolescents the dosage should be adapted to the patient's weight at 150 mg/kg twice or thrice daily to a maximum daily dose of 12 g.

DO NOT USE if packet is swollen or the granules have lost their tan color, turning dark brown or purple.

## SIDE EFFECTS

*Blood and the lymphatic system disorders:*

Less frequent: Antiglobulin positive haemolytic anaemia in patients with G6PD deficiency. Megaloblastic anaemia due to vitamin $B_{12}$ deficiency.

*Immune system disorders*

Frequent: Hypersensitivity reactions: Fever, skin rashes or itching, eosinophilia, leucocytosis.

Less frequent: Hypersensitivity reactions: arthralgia, lymphadenopathy, hepatosplenomegaly, infectious mononucleosis-like or lymphoma-like syndrome, jaundice, encephalopathy, leucopenia, agranulocytosis, thrombocytopenia, pericarditis, hypoglycaemia, optic neuritis, eosinophylic pneumonia, vasculitis, and reduction in prothrombin.

*Metabolism and nutrition disorders:*

Less frequent: Vitamin $B_{12}$ deficiency, iron deficiency, depressed cholesterol.

*Endocrine disorders*

Less frequent: Goitre and hypothyroidism.

*Psychiatric disorders*

Less frequent: Psychosis*.

*Although there are no reports of psychosis directly related to PASER, psychiatric disorders were observed during treatment of MDR-TB with combination of anti-tuberculosis agents.

Patients on MDR-TB therapy of more than one month should be considered for maintenance Vitamin $B_{12}$.

*Gastrointestinal disorders:*

Frequent: Nausea, vomiting, diarrhoea and abdominal pain.

*Hepato-biliary disorders:*

Less frequent: Hepatitis, steatorrhoea.

*Renal and urinary disorders*

Less frequent: Crystalluria (may be prevented by the maintenance of urine at a neutral or alkaline pH).

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

Overdose has not been reported. In overdose, side effects will be exacerbated and exaggerated (see SIDE EFFECTS).

Treatment is symptomatic and supportive.

**IDENTIFICATION**

Light tan coloured, spherical shaped, odourless coated granules.

**PRESENTATION**

Carton of 30 packets. The packets are white, opaque and consist of paper, aluminium and LDPE layers.

Each packet contains 4 grams p-aminosalicylic acid.

**STORAGE INSTRUCTIONS**

Store at or below 25 °C for up to 24 months.

AVOID EXCESSIVE HEAT. DO NOT USE if packet is swollen or the granules have lost their tan colour, turning dark brown or purple.

Any unused granules after initially opening the sachet must be discarded.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

**REGISTRATION NUMBER**

45/20.2.3/0037

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive, Route 21 Corporate Park

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**DATE OF PUBLICATION OF THE PACKAGE INSERT**

Date of Registration: 05 August 2011

Date of latest revision of the text: 17 September 2019

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| Namibia: NS2<br>Reg. Nr. : 10/20.2.3./0484 |