1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PURDERAL P 100 mg tablets

PURDERAL P 400 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PURDERAL P 100 mg tablet contains 100 mg of ethambutol hydrochloride.

Contains sugar: Lactose monohydrate 26,8 mg

Each PURDERAL P 400 mg tablet contains 400 mg of ethambutol hydrochloride.

Contains sugar: Lactose monohydrate 107,2 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

PURDERAL P 100 mg tablets: A yellow, film-coated, round, biconvex tablet with bevelled edges, debossed with E31 on one side and plain on the other side.

PURDERAL P 400 mg tablets: A grey, film-coated, round, biconvex tablet with bevelled edges, debossed with E71 on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PURDERAL P is indicated for the treatment of tuberculosis in combination with other antituberculosis medicines.

Consideration should be given to the current local guidelines for treatment of tuberculosis.

4.2 Posology and method of administration

Posology

In the treatment of tuberculosis, serum concentrations of 3 to 5 µg per ml of ethambutol, as contained in PURDERAL P, are considered necessary and they are generally attained with a dose of 15 to 25 mg per kg body weight daily. A single dose of 25 mg per kg may be given for 2 months and thereafter reduced to 15 mg per kg. It has been suggested that tests of visual acuity should be regularly performed on patients being treated with ethambutol, as contained in PURDERAL P (see section 4.8).

Adult dose

The dosage must be adjusted according to the body mass of the patient - refer to the table of dosages.

For primary treatment

PURDERAL P should be administered in a single daily oral dose of 15 mg/kg with concomitant medicines being used at their recommended dosage levels.

For re-treatment

For the first 60 days of treatment, PURDERAL P should be administered in a single daily oral dose of 25 mg/kg. Thereafter the dosage should be reduced to 15 mg/kg with

concomitant medicines being maintained at their recommended dosage levels.

Paediatric population

Daily doses for children above three months are 20 (15 to 25) mg/kg per body-weight daily.

No dosing recommendation can be made in children less than three months due to the lack of specific data. PURDERAL P is not recommended for children under 13 years of age.

Method of administration

Examples of dosage and administration of PURDERAL P tablets are shown in the table below:

15 mg/kg schedule				***25 mg/kg schedule***			
Mass range (kg)	***Total daily dosage (mg)***	***Number of tablets 100mg***	***400mg***	***Mass range (kg)***	***Total daily dosage (mg)***	***Number of tablets 100mg***	***400mg***
Under 37	500	1	1	Under 38	900	1	2
38 to 42,5	600	2	1	38 to 41,5	1 000	2	2
43 to 49,5	700	3	1	42 to 44,5	1 100	3	2
50 to 56,5	800		2	45 to 49,5	1 200		3
57 to 63,5	900	1	2	50 to 53,5	1 300	1	3
64 to 70,5	1 000	2	2	54 to 57,5	1 400	2	3
71 to 78,5	1 100	3	2	58 to 61,5	1 500	3	3
79 to 83,5	1 200		3	62 to 66,5	1 600		4
84 to 89,5	1 300	1	3	67 to 70,5	1 700	1	4
90 to 96,5	1 400	2	3	71 to 74,5	1 800	2	4

97 and over	1 500	3	3	75 to 78,5	1 900	3	4
				79 to 82,5	2 000		5
				83 to 86,5	2 100	1	5
				87 to 90,5	2 200	2	5
				91 to 94,5	2 300	3	5
				95 to 98,5	2 400		6
				99 and over	2 500	1	6

4.3 Contraindications

PURDERAL P is contraindicated in patients with:

- Hypersensitivity to ethambutol or to any of the excipients in PURDERAL P (see section 6.1).
- Severe renal impairment (creatinine clearance GFR < 30 mL/min).
- Optic neuritis and retrobulbar neuritis.

4.4 Special warnings and precautions for use

Consideration should be given to current local guidelines for the treatment of tuberculosis.

Optic neuritis

Ethambutol, as contained in PURDERAL P, can cause optic neuritis (ON), which may be unilateral or bilateral, and retrobulbar ON (normal appearing optic disc on presentation) is the most common form of ethambutol-induced optic neuritis (EON).

EON is dose dependent with a prevalence ranging from < 1 % at ≤ 15 mg/kg, to 5 % to 6 % at ≤ 25 mg/kg. Other risk factors include patient on prolonged therapy, patients with renal impairment, the elderly and use with isoniazid. It is recommended that patients

undergo a full ophthalmic examination before starting treatment. This should include visual acuity, colour vision, perimetry and ophthalmoscopy. Except for the high risk patients (see below), routine ophthalmological examination for adults is not thereafter necessary. Patients should be informed of the importance of reporting any change in vision and PURDERAL P should be withdrawn if vision deteriorates.

For patients with risk factors for development of EON, frequent ophthalmologic examination is recommended.

Each eye should be tested separately as ocular toxicity can be unilateral or bilateral. Ophthalmologic examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy.

Routine ophthalmological examinations may be considered when treating young children.

Prognosis:

The vision impairment (optic neuritis) is generally reversible when administration of ethambutol, as in PURDERAL P, is discontinued promptly. Studies have shown that the recovery of visual acuity took weeks to months after the ethambutol, as contained in PURDERAL P, was discontinued. Ethambutol, as contained in PURDERAL P, was restarted in some patients at lower doses without toxicity.

Recovery may be delayed for up to one year or more or the effects may be irreversible.

Renal impairment and hyperuricemia

Renal function, including uric acid levels, should be checked before treatment with PURDERAL P and appropriate dosage adjustments made.

PURDERAL P should preferably be avoided in patients with renal impairment and hyperuricemia, but if used the dose should be reduced. Toxic effects and hyperuricemia are more common if renal function is impaired.

PURDERAL P therapy results in an increased concentration of urate in the blood in about 50 % of patients, due to decreased renal excretion of uric acid. The effects may be detectable as early as 24 hours after a single dose or as late as 90 days after treatment is started. This untoward effect is possibly enhanced by isoniazid and pyridoxine.

Excipients

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take PURDERAL P.

4.5 Interaction with other medicines and other forms of interaction

Aluminum hydroxide

Aluminium hydroxide impairs the absorption of ethambutol.

The results of a study of coadministration of ethambutol hydrochloride (50 mg/kg) with an aluminum hydroxide containing antacid to 13 patients with tuberculosis showed a reduction of mean serum concentrations and urinary excretion of ethambutol of approximately 20 % and 13 %, respectively, suggesting that the oral absorption of ethambutol may be reduced by these antacid products. It is recommended to avoid concurrent administration of PURDERAL P with aluminum hydroxide-containing antacids for at least 4 hours following PURDERAL P administration (see section 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are no know adverse effects of ethambutol, as contained in PURDERAL P, on the reproductive potential of women of childbearing potential.

Pregnancy

The safety of PURDERAL P in pregnancy and lactation has not been established.

The potential for risk in humans is unknown as there are no adequate and well controlled studies in pregnant women. Studies in animals have shown reproductive toxicity.

Breastfeeding

Ethambutol hydrochloride, as contained in PURDERAL P, is excreted into breast milk. Ethambutol/metabolites have been identified in breastfed newborns/ infants of treated women. Breastfeeding is not recommended during PURDERAL P treatment.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

PURDERAL P has moderate influence on the ability to drive and operate machinery.

Since adverse reactions such as visual disturbances have been reported in patients receiving PURDERAL P, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that PURDERAL P does not adversely affect their ability to do so (see section 4.4 and 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most important side effect of ethambutol hydrochloride, as contained in PURDERAL P, is a dose dependant optic neuritis, resulting in decrease of visual acuity and loss of ability to perceive the colour green.

This is quite uncommon (< 1 %) with a dose ≤ 15 mg/kg per day, but increases to 5 % to 6 % with doses ≤ 25 mg/kg per day.

b) Tabulated list of adverse reactions

System organ class	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders	Thrombocytopenia, leucopenia, neutropenia, eosinophilia	
Immune system disorders	Hypersensitivity, anaphylactoid reactions, allergic reactions, anaphylaxis, allergic pneumonitis	
Metabolism and nutrition disorders	Hyperuricaemia	Gout
Psychiatric disorders		Mental confusion, disorientation, hallucinations
Nervous system disorders	Peripheral neuropathy, numbness, paraesthesia of the extremities, headache, dizziness, burning pain, weakness (hands and feet), disorientation, tremor	
Eye disorders	Optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain)	
Respiratory, thoracic and mediastinal disorders	Pneumonitis, pulmonary infiltrates, with or without eosinophilia	

Gastrointestinal disorders	Anorexia, nausea, vomiting, abdominal pain, diarrhoea, flatulence, metallic taste, loss of appetite, upset stomach	
Hepato-biliary disorders	Hepatic reactions with hepatitis, jaundice, abnormal liver function test values, hepatic failure	
Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria, photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis	
Musculoskeletal and connective tissue disorders	Joint pains	
Renal and urinary disorders	Interstitial nephritis, nephrotoxicity	
General disorders and administrative site conditions	Malaise, pyrexia	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

The symptoms of overdosage are those stated under side effects above and in these cases the dosage should be reduced or the medicine discontinued.

Treatment

There is no specific antidote. Treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.2.3 Tuberculostatics.

Pharmacotherapeutic group: Other drugs for treatment of tuberculosis

ATC code: J04AK02

Mechanism of action

Ethambutol is bacteriostatic. It is effective against *Mycobacterium tuberculosis* and *M. bovis* with an MIC of 0,5 to 8 µg/mL. While it has activity against some atypical mycobacteria including *M. Kansarii*, activity against other microorganisms has not yet been reported. It is effective against tubercle bacilli resistant to other tuberculostatics. Cross-resistance has not yet been reported. Primary resistance to ethambutol is uncommon but resistant strains of *M. tuberculosis* are readily produced if ethambutol is used alone.

5.2 Pharmacokinetic properties

Absorption

About 75 % to 80 % of an orally administered dose of ethambutol is absorbed from the gastrointestinal tract. Plasma concentrations are maximal in man 2 to 4 hours after the medicine is taken and are proportional to the dose.

Absorption is not significantly impaired by food.

Distribution

A single dose of 25 mg/kg produces a plasma concentration of about 5 µg/ml at 2 hours. Ethambutol has a relatively long half-life; about 50 % of the peak concentration is present in the blood at 8 hours and less than 10 % at 24 hours. It has also been reported to cross the placenta.

Biotransformation

The medicine enters erythrocytes with ease; 1 hour after an intravenous dose two to three times as much ethambutol is present in the erythrocytes as in the plasma. Red blood cells thereby serve as a depot from which the medicine slowly enters the plasma.

Elimination

Within 24 hours 50 % of an ingested dose of ethambutol is excreted unchanged in the urine; up to 15 % is excreted in the form of two metabolites, an aldehyde and a dicarboxylic acid is excreted by tubular secretion or solely by glomerular filtration, the latter is thought to play the primary role.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicone dioxide (Aerosil), croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose 101, povidone K25.

Coating:

PURDERAL P 100 mg (tablets): Dye Opadry II Yellow.

PURDERAL P 400 mg (tablets): Dye Opadry HP II Grey.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep in the original packaging until required for use.

6.5 Nature and contents of container

PURDERAL P 100 mg tablets: Pack sizes of 100 and 1 000 tablets.

PURDERAL P 100 mg tablets are packed in blister strips containing 10 tablets per strip.

The blister strips are packed into cardboard cartons imprinted with text.

PURDERAL P 100 mg tablets are also packed in securitainers with a cap, foam insert and silica gel sachet.

PURDERAL P 400 mg tablets: Pack sizes of 100 and 1 000 tablets.

PURDERAL P 400 mg tablets are packed in blister strips containing 10 tablets per strip.

The blister strips are packed into cardboard cartons imprinted with text.

PURDERAL P 400 mg tablets are also packed in securitainers with a cap, foam insert.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8 REGISTRATION NUMBER

PURDERAL P 100 mg: J/20.2.3/261

PURDERAL P 400 mg: J/20.2.3/262

9 DATE OF FIRST AUTHORISATION

11 March 1977

10 DATE OF REVISION OF TEXT

7 June 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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