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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ETHAMBUTOL 400 mg PD film coated tablets

ETHAMBUTOL 100 mg ODT PD oral dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ETHAMBUTOL 400 mg PD: Each film coated tablet contains ethambutol hydrochloride 400 mg.

Sugar free.

ETHAMBUTOL 100 mg ODT PD: Each oral dispersible tablet contains ethambutol hydrochloride 100 mg.

Sugar free.

Contains sweetener (aspartame 20,0 mg per tablet).

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ETHAMBUTOL 400 mg PD: Film coated tablets.

Light orange coloured, round, biconvex film coated tablets plain on both sides.

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ETHAMBUTOL 100 mg ODT PD: Uncoated oral dispersible tablet

White to off-white, Round, uncoated tablets. They are flat on the top and bottom with a bevelled edge. The tablets have a break line on one side and are plain on the other side with characteristic odour.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ETHAMBUTOL PD is indicated for the treatment of tuberculosis in combination with other anti-tubercular medicines, in adults and children over 5 years of age. Consideration should be given to the current local guidelines for treatment of tuberculosis.

4.2 Posology and method of administration

Posology

ETHAMBUTOL PD should not be used alone in the initial treatment or in re-treatment.

Therapy in general should be continued until bacteriological conversion has become permanent and maximal clinical improvement has occurred.

In the treatment of tuberculosis, serum concentrations of 3 - 5 µg per mL of ethambutol, as contained in ETHAMBUTOL PD, are considered necessary and they are generally attained with a dose of 15 - 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 ETHAMBUTOL PD (see section 4.8).

Adults

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

For primary treatment:

The usual adult dose of ETHAMBUTOL PD is 15 mg/kg given once a day, with concomitant medicines being used at their recommended dosage levels.

For re-treatment:

For the first 60 days of treatment, ETHAMBUTOL PD should be administered in a single daily 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

No dosing recommendation can be made in children less than 5 years of age due to the lack of specific data (see section 4.3).

Special populations

Renal impairment:

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ETHAMBUTOL PD accumulates in patients with impaired renal function and adjustment of dosage is necessary.

Elderly:

Dosage as for adults.

Method of administration

For oral use. ETHAMBUTOL PD can be taken with or without food.

Examples of dosage and administration of ETHAMBUTOL PD 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**		**Mass range (kg)**	**Total daily dosage (mg)**	**Number of tablets**	
		100 mg	**400 mg**			**100 mg**	**400 mg**
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	13	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

See section 6.6 for the instructions for preparation of the dispersible tablet for administration.

Missed dose:

Doctors should advise patients who forget to take ETHAMBUTOL PD to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

ETHAMBUTOL PD is contraindicated in patients with:

- hypersensitivity to ethambutol or to any of the ingredients of ETHAMBUTOL PD (see section 6.1)
- severe renal impairment (creatinine clearance GFR < 30 mL/min)
- in patients with known optic neuritis and retrobulbar neuritis .

ETHAMBUTOL 400 mg PD is contraindicated in children under 5 years of age.

4.4 Special warnings and precautions for use

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

Ocular toxicity:

Ethambutol, as contained in ETHAMBUTOL PD, may produce decreases in visual acuity which appear to be due to optic neuritis.

This is generally reversible and to be related to dose and duration of treatment.

Visual changes 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 - 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. Each eye must be tested separately and both eyes together. It should also be given with great care in patients with reduced visual acuity, such as the elderly, and in children in whom evaluation of changes in visual acuity may be difficult. Tests of visual acuity and red-green discrimination prior to the start of therapy, and periodically thereafter, are strongly recommended and ETHAMBUTOL PD should be withdrawn if vision deteriorates.
Any change may be unilateral or bilateral and hence both eyes should be tested individually.

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.
Except for the high-risk patients (see below), routine ophthalmological examination for adults is not necessary thereafter. Patients should be informed of the importance of reporting any change in vision and ETHAMBUTOL PD should be withdrawn if vision deteriorates.
For patients with risk factors for development of EON, frequent ophthalmologic examination is recommended.

Routine ophthalmological examination for adults is not thereafter necessary, but patients should be informed of the importance of reporting any change in vision.

Routine ophthalmological examinations may be considered desirable when treating young children.

Prognosis:

This effect is generally reversible when administration of ETHAMBUTOL PD is discontinued promptly. However, irreversible blindness has been reported.
Studies have shown that the recovery of visual acuity took weeks to months after the ethambutol, as contained in ETHAMBUTOL PD, was discontinued. Ethambutol, as contained in ETHAMBUTOL PD, was restarted in some patients at lower doses without toxicity.

In rare cases, recovery may be delayed for up to one year or more or the effects may be irreversible.

Renal impairment and hyperuricaemia

Toxic effects are more common if renal function is impaired.
Renal function, including uric acid levels, should be checked before treatment with ETHAMBUTOL PD and appropriate dosage adjustments made.
ETHAMBUTOL PD should preferably be avoided in patients with renal impairment and hyperuricaemia, but if used the dose should be reduced. Toxic effects and hyperuricaemia are more common if renal function is impaired.
ETHAMBUTOL PD 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.

Use of ETHAMBUTOL PD should be carefully considered in patients with a history of gout. ETHAMBUTOL PD may precipitate attacks of gout.

Hepatic impairment:

Liver function tests should be performed in patients who develop symptoms suggestive of hepatitis or who become generally unwell during treatment with ETHAMBUTOL PD. Serum concentrations of ethambutol should not exceed 5 µg/mL.

Other:

Consideration should be given to current clinical guidance on the appropriate use of anti-tuberculous medicines.

Skin and subcutaneous tissue disorders

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with ethambutol treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, ethambutol should be

withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of ethambutol, treatment with ethambutol must not be restarted in this patient at any time.

In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider the possibility of a reaction to ethambutol in children that develop symptoms of rash and fever during therapy with ethambutol.

4.5 Interaction with other medicines and other forms of interaction

Concurrent administration of ETHAMBUTOL 400 mg PD with other neurotoxic medicines may increase the potential for neurotoxicity, such as optic and peripheral neuritis.

Aluminium hydroxide

Aluminium containing antacids impairs the absorption of ethambutol.

The results of a study of co-administration of ethambutol hydrochloride (50 mg/kg) with an aluminium 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 ETHAMBUTOL PD with aluminium hydroxide-containing antacids

for at least 4 hours following ETHAMBUTOL PD administration (see section 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are no known adverse effects of ethambutol, as contained in ETHAMBUTOL PD, on the reproductive potential of women of childbearing potential.

Pregnancy

The safety of ETHAMBUTOL PD in pregnancy 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.

Ethambutol is not recommended during pregnancy.

Breastfeeding

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

Teratogenic effects have been seen in animals.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Visual disturbances associated with retrobulbar optic neuritis causing a restriction in visual acuity, constriction of visual field, dark spots in the visual field, red-green colour blindness are the most important side effects of ETHAMBUTOL 400 mg PD when considering the patient's ability to safely drive or operate machinery (see sections 4.3, 4.4 and 4.8). These effects on sharpness of sight, clarity of vision, field of vision, and impaired red-green colour vision should be borne in mind when considering the patient's ability to safely drive or operate machinery.
Dizziness, disorientation, numbness and paraesthesia are also among possible side effects that may affect a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most important side effect of ethambutol hydrochloride, as contained in ETHAMBUTOL PD, is dose-dependent optic neuritis, resulting in a decrease of visual acuity and loss of ability to perceive the colour green.
This is less frequent (< 1 %) with a dose ≤ 15 mg/kg per day, but increases to 5 % to 6 % with doses ≤ 25 mg/kg per day.

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, leukopenia, neutropenia, eosinophilia

Immune system disorders	Less frequent	Hypersensitivity (such as fever, skin rash, nausea), anaphylactoid reactions, allergic reactions, anaphylaxis, allergic pneumonitis
Metabolism and nutrition disorders	Less frequent	Hyperuricaemia, gout
Psychiatric disorders	Less frequent	Mental confusion, hallucinations
Nervous system disorders	Less frequent	Peripheral neuropathy, headache, dizziness, numbness, paraesthesia of the extremities, burning pain, weakness (hands and feet), disorientation, tremor
Eye disorders	Less frequent	Retrobulbar optic neuritis causing a restriction in visual acuity, constriction of visual field, dark spots in the visual field, red-green colour blindness, loss of vision, eye pain, retinal haemorrhage, scotoma, visual disturbance
Respiratory, thoracic and mediastinal disorders	Less frequent	Pneumonitis, pulmonary infiltrates, with or without eosinophilia

Gastrointestinal disorders	Less frequent	Nausea, vomiting, anorexia, abdominal pain and gastrointestinal upset (diarrhoea), flatulence, metallic taste, loss of appetite, upset stomach
Hepato-biliary disorders	Less frequent	Jaundice, liver toxicity, abnormal liver function test values, hepatic reactions with hepatitis, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Rash, pruritus, urticaria, photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)
Musculoskeletal, connective tissue and bone disorders	Less frequent	Joint pains
Renal and urinary disorders	Less frequent	Interstitial nephritis, nephrotoxicity
General disorders and administrative site conditions	Less frequent	Malaise, fever (pyrexia)

Description of selected adverse reactions

Visual disturbances may be unilateral or bilateral; therefore, each eye should be tested separately (see section 4.4). Typical signs include: blurred vision, eye pain,

impairment of colour vision (red-green colour blindness), constriction of visual field (central or peripheral scotoma), and any loss in vision. Recovery of visual acuity has usually occurred over a period of weeks to months after the drug was discontinued, and patients have then received Ethambutol at lower dosage without toxicity.
Liver function tests should be performed in patients who develop symptoms suggestive of hepatitis or who become generally unwell during treatment. Hepatic reactions with hepatitis, jaundice, abnormal liver function test values, and very rarely, hepatic failure, have been reported in patients treated with multiple drug therapy including ethambutol. Liver function tests should be performed in patients who develop symptoms suggestive of hepatitis or who become generally unwell during treatment.

Gastrointestinal disorders such as anorexia, nausea, vomiting, abdominal pain and diarrhoea have been noted in patients on multiple drug anti-tuberculosis therapy including ethambutol although not in test patients receiving ethambutol as sole therapy.

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 professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Symptoms of overdosage may be any of those listed under section 4.8 above.

Typically, symptoms include gastrointestinal disturbances, vomiting, fever, headache, anorexia, dizziness, hallucinations and/or visual disturbances. In these cases the dosage should be reduced or the medicine discontinued.

Management of overdose:

Changes in visual acuity should be carefully evaluated and if necessary the administration of ETHAMBUTOL PD should be discontinued.

Blood concentrations of ETHAMBUTOL PD after overdosage may be reduced by haemodialysis or peritoneal dialysis.

There is no specific antidote, supportive and symptomatic treatment should be employed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for treatment of tuberculosis

ATC code: J04AK02

Pharmacological classification: A 20.2.3. Antimicrobial (chemotherapeutic) agents, Tuberculostatics

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Mechanism of action

Ethambutol is bacteriostatic. It is effective against *Mycobacterium tuberculosis* and *M. bovis* with a minimum inhibitory concentration (MIC) of 0,5 - 8 µ/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.

Mechanism of Resistance

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:

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About 75 - 80 % of an oral 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:

After a single dose of 25 mg/kg produces peak plasma concentrations of up to 2 – 5 µg/ml appear within 2 – 4 hours, and are less than 1 µg/ml by 24 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. Ethambutol is distributed to most

tissues, including the lungs, kidneys and erythrocytes. It has been reported to cross the placenta and is distributed into breast milk.

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

ETHAMBUTOL 400 mg PD:

Cores:

Colloidal silicon dioxide

Magnesium stearate

Maize starch

Povidone

Purified talc

Film coating:

Ethyl cellulose

Hypromellose

Lake of sunset yellow

Propylene glycol

Polyethylene glycol

Purified talc

Titanium dioxide

ETHAMBUTOL 100 mg ODT PD:

Aspartame

Colloidal silicon dioxide

Croscarmellose sodium

Crospovidone

Flavour orange SD2912 (containing flavouring preparations, maltodextrin and gum acacia, and a nature-identical flavouring substance)

Low substituted hydroxy propyl cellulose

Magnesium stearate

Maize starch

Microcrystalline cellulose

Povidone

Silicified microcrystalline cellulose

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from heat and moisture.

Do not remove the blisters from the outer carton until required for use.

HDPE containers: Keep well closed.

6.5 Nature and contents of container

ETHAMBUTOL 400 mg PD:

Clear PVC/PVDC/aluminium blister strips of 10 tablets each, available in packs of 100 in an outer carton.

Clear PVC/PVDC/aluminium blister strips of 28 tablets, available in packs of 56 or 84 tablets in an outer carton.

Or

White round HDPE containers with a white HDPE cap containing 100 or 1 000 tablets.

ETHAMBUTOL 100 mg ODT PD:

Aluminium strip containing aluminium foil 0,04 mm as a base material and plain strip

aluminium foil 0,04 mm as a lidding material.

Pack sizes: 10/30/60/90/100/120/180’s

Not all pack sizes are marketed.

6.6 Special precautions for disposal

1. The required amount of drinking water should be poured into a small, clean drinking container such as a tumbler or cup

2. The required number of tablets should be added to the container.

3. The container should be swirled until tablets disperse completely, and the patient should drink the entire mixture immediately.

4. The container should be rinsed with an additional 10 mL of water, which the patient should drink to ensure that the entire dose is taken.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

ETHAMBUTOL 400 mg PD: A45/20.2.3/0518

ETHAMBUTOL 100 mg ODT PD: 60/20.2.3/0390

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ETHAMBUTOL 400 mg PD:

Date of registration: 10 April 2014

Date of latest approval: 18 July 2017

ETHAMBUTOL 100 mg ODT PD:

Date of registration: 07 July 2026

10. DATE OF REVISION OF THE TEXT

07 July 2026