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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DYNA ETHAMBUTOL 400 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains ethambutol hydrochloride 400 mg.

DYNA ETHAMBUTOL 400 mg is sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DYNA ETHAMBUTOL 400 mg is indicated for the treatment of tuberculosis in combination with other anti-tubercular medicine, in adults and children over 12 years of age.

4.2 Posology and method of administration

DYNA ETHAMBUTOL 400 mg 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.

Adults and children over 12 years:

The dosage must be adjusted according to the body mass of the patient.

Adults:

For primary treatment:

The usual adult dose of DYNA ETHAMBUTOL 400 mg 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, DYNA ETHAMBUTOL 400 mg 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.

Special populations

Renal impairment:

DYNA ETHAMBUTOL 400 mg accumulates in patients with impaired renal function and adjustment of dosage is necessary.

Elderly:

Dosage as for adults.

Paediatric population

DYNA ETHAMBUTOL 400 mg is not recommended for use in children under 5 years.

Method of administration

For oral use. DYNA ETHAMBUTOL 400 mg can be taken with or without food.

Missed dose:

Doctors should advise patients who forget to take DYNA ETHAMBUTOL 400 mg 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

- Hypersensitivity to ethambutol or to any of the ingredients of DYNA ETHAMBUTOL 400 mg (see section 6.1)
- in patients with known optic neuritis
- children under 5 years of age.

4.4 Special warnings and precautions for use

Ocular toxicity:

DYNA ETHAMBUTOL 400 mg may produce decreases in visual acuity which appear to be due to optic neuritis. Visual changes may be unilateral or bilateral. This effect is generally reversible when administration of DYNA ETHAMBUTOL 400 mg is discontinued promptly. However, irreversible blindness has been reported. 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 DYNA ETHAMBUTOL 400 mg should be withdrawn if vision deteriorates.

Gout:

Use of DYNA ETHAMBUTOL 400 mg should be carefully considered in patients with a history of gout. DYNA ETHAMBUTOL 400 mg may precipitate attacks of gout.

Renal impairment:

DYNA ETHAMBUTOL 400 mg should be given in reduced dosage to patients with renal impairment and dosage adjustments may be needed according to serum concentrations.

Hepatic impairment:

Liver function tests should be performed in patients who develop symptoms suggestive of hepatitis or who become generally unwell during treatment with DYNA ETHAMBUTOL

400 mg. 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.

4.5 Interaction with other medicines and other forms of interaction

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

Aluminium containing antacids may delay the absorption of DYNA ETHAMBUTOL 400 mg. Avoid concurrent administration of DYNA ETHAMBUTOL 400 mg with aluminium containing antacids for at least 4 hours.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of DYNA ETHAMBUTOL 400 mg in pregnancy and lactation has not been established.

Breastfeeding

DYNA ETHAMBUTOL 400 mg crosses the placenta and is excreted in breast milk.

Teratogenic effects have been seen in animals.

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 DYNA ETHAMBUTOL 400 mg when considering the patient's ability to safely drive or operate machinery (see section 4.8).

Dizziness, disorientation, numbness and paraesthesia are also among possible side effects that may affect a patient's ability to drive or operate machinery.

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.

4.8 Undesirable effects

Summary of the safety profile

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, leucopenia, neutropenia
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity (such as fever; skin rash, nausea) Anaphylactic reactions
Metabolism and nutrition disorders	Less frequent	Hyperuricaemia, precipitation of gout

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Psychiatric disorders	Less frequent	Disorientation, mental confusion, possible hallucinations
Nervous system disorders	Less frequent Frequency unknown	Headache, dizziness, numbness and tingling of the extremities due to peripheral neuritis, peripheral neuropathy, burning pain, weakness (hands and feet) Tremor
Eye disorders	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
Vascular disorders	Less frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Pneumonitis, pulmonary infiltrates, with or without eosinophilia
Gastrointestinal disorders	Less frequent Frequency unknown	Nausea, vomiting, anorexia, abdominal pain and gastrointestinal upset (diarrhoea) Flatulence, metallic taste, loss of appetite, upset stomach
Hepatobiliary disorders	Less frequent Frequency unknown	Jaundice Liver toxicity, transient and asymptomatic elevations in liver function tests, hepatic reactions with hepatitis, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria, photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Less frequent	Joint pain

Renal and urinary disorders	Less frequent	Interstitial nephritis
General disorders and administrative site conditions	Less frequent	Malaise, fever

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.

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 asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

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.

Management of overdose:

Changes in visual acuity should be carefully evaluated and if necessary the administration of DYNA ETHAMBUTOL 400 mg should be discontinued.

Blood concentrations of DYNA ETHAMBUTOL 400 mg after overdosage may be reduced by haemodialysis or peritoneal dialysis.

There is no specific antidote, but gastric lavage should be employed if necessary followed by supportive and symptomatic treatment.

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

Mechanism of action

Ethambutol is a synthetic, bacteriostatic antitubercular medicine. Ethambutol inhibits aribinosyl transferase III, thereby disrupting the transfer of arabinose into arabinogalactan biosynthesis which in turn disrupts the assembly of mycobacterial cell wall. The aribinosyl transferases are encoded by *embAB* genes.

Ethambutol has activity against a wide range of mycobacteria but has no activity against any other genus. The MICs are 0,5 – 2 mg/l in clinical isolates of *M. tuberculosis*, approximately 0,8 mg/l for *M. kansaii* and 2 - 7,5 mg/l for *M. avium*.

In vitro, mycobacterial resistance to ethambutol develops via mutations in the *embB* gene. In 30 – 70 % of clinical isolates that are resistant to ethambutol, mutations are encountered in ethambutol-susceptible mycobacteria, as though this mutation is necessary, but not sufficient, to confer ethambutol resistance. In addition, enhanced efflux pump activity may induce resistance to both isoniazid and ethambutol in the laboratory.

5.2 Pharmacokinetic properties

Absorption:

About 80 % of an oral dose of ethambutol is absorbed from the gastrointestinal tract. Absorption is not significantly impaired by food.

Distribution:

After a single dose of 25 mg/kg 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 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 and elimination:

The elimination half-life after oral doses is about 3 to 4 hours.

Within 24 hours, 75 % of an ingested dose of ethambutol is excreted unchanged in the urine; up to 15 % is excreted in the form of two inactive metabolites, an aldehyde and a dicarboxylic acid derivative.

About 20 % of the dose is excreted unchanged in the faeces. Ethambutol is excreted by tubular secretion in addition to glomerular filtration.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a dry place at or below 30 °C.

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

HDPE containers: Keep well closed.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER

A45/20.2.3/0518

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 10 April 2014

Date of latest approval: 18 July 2017

10. DATE OF REVISION OF THE TEXT

To be allocated by Council