PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ETHAMBUTOL 400 mg PHARMA-Q film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains ethambutol hydrochloride 400 mg.

Contains sugar: sorbitol 2,8 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

White to off white, smooth, round, biconvex, film-coated tablets, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ETHAMBUTOL 400 mg PHARMA-Q is indicated for the treatment of tuberculosis in conjunction with other anti-tuberculosis medicines.

Consideration should be given to the current local guidelines for the 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 ETHAMBUTOL 400 mg PHARMA-Q, 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 ETHAMBUTOL 400 mg PHARMA-Q (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:

ETHAMBUTOL 400 mg PHARMA-Q 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, ETHAMBUTOL 400 mg PHARMA-Q 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:

Daily doses for children above three months are 20 (15-25) mg/kg per bodyweight daily. No dosing recommendation can be made in children less than three months due to lack of specific data. ETHAMBUTOL 400 mg PHARMA-Q is not recommended for children under 13 years of age.

Examples of dosage and administration of ETHAMBUTOL 400 mg PHARMA-Q 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	-	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

Method of administration

Oral use.

4.3 Contraindications

ETHAMBUTOL 400 mg PHARMA-Q is contraindicated in patients with:

- Hypersensitivity to ethambutol or to any of the excipients in ETHAMBUTOL 400 mg PHARMA-Q (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 ETHAMBUTOL 400 mg PHARMA-Q, 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 patients 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 ETHAMBUTOL 400 mg PHARMA-Q 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 ETHAMBUTOL 400 mg PHARMA-Q, is discontinued promptly. Studies have shown that the recovery of visual acuity took weeks to months after the ethambutol,

as contained in ETHAMBUTOL 400 mg PHARMA-Q, was discontinued. Ethambutol, as contained in ETHAMBUTOL 400 mg PHARMA-Q, 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 ETHAMBUTOL 400 mg PHARMA-Q and appropriate dosage adjustments made.

ETHAMBUTOL 400 mg PHARMA-Q 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.

ETHAMBUTOL 400 mg PHARMA-Q 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.

Excipient warning

ETHAMBUTOL 400 mg PHARMA-Q contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take ETHAMBUTOL 400 mg PHARMA-Q.

4.5 Interaction with other medicines and other forms of interaction

Aluminium hydroxide reduces the absorption of ethambutol. It is recommended to avoid concurrent administration of ETHAMBUTOL 400 mg PHARMA-Q with aluminium hydroxide-containing antacids for at least 4 hours following ETHAMBUTOL 400 mg PHARMA-Q administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

There are no know adverse effects of ethambutol, as contained in ETHAMBUTOL 400 mg PHARMA-Q, on the reproductive potential of women of childbearing potential.

Pregnancy

The safety of ETHAMBUTOL 400 mg PHARMA-Q 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 ETHAMBUTOL 400 mg PHARMA-Q, is excreted into ~~the~~ breast milk. Ethambutol/metabolites have been identified in breastfed newborns/ infants of treated women. Breastfeeding is not recommended during treatment with ETHAMBUTOL 400 mg PHARMA-Q.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

ETHAMBUTOL 400 mg PHARMA-Q has a moderate influence on the ability to drive and operate machinery. Patients whose vision is impaired during treatment with ETHAMBUTOL 400 mg PHARMA-Q should not drive or operate machinery.

Patients should not drive or operate machinery if affected by possible side effects such as numbness, paraesthesia, dizziness and disorientation.

4.8 Undesirable effects

a. Summary of the safety profile

The most important side effect of ethambutol hydrochloride, as contained in ETHAMBUTOL 400 mg PHARMA-Q, 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 summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, leucopenia, neutropenia, eosinophilia
Immune system disorders	Less frequent	Hypersensitivity, anaphylactoid reactions, allergic reactions, anaphylaxis, allergic pneumonitis
Metabolism and nutrition disorders	Less frequent	Hyperuricaemia
	Frequency unknown	Gout
Psychiatric disorders	Frequency unknown	Mental confusion, disorientation, hallucinations
Nervous system disorders	Less frequent	Peripheral neuropathy, paraesthesia (especially in the extremities), numbness, disorientation, dizziness, headache, burning pain, weakness (hands and feet), tremor

MedDRA system organ class	**Frequency**	**Adverse reactions**
Eye disorders	Less frequent	Optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain)
Respiratory, thoracic and mediastinal disorders	Less frequent	Pneumonitis, pulmonary infiltrates, with or without eosinophilia
Gastrointestinal disorders	Less frequent	Nausea, vomiting, anorexia, flatulence, abdominal pain, diarrhoea, metallic taste, loss of appetite, upset stomach
Hepato-biliary disorders	Less frequent	Hepatic reactions with hepatitis, jaundice, abnormal liver function test values, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria, photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis
Musculoskeletal and connective tissue disorders	Less frequent	Joint pains
Renal and urinary disorders	Less frequent	Interstitial nephritis, nephrotoxocity

MedDRA system organ class	Frequency	Adverse reactions
General disorders and administration site conditions:	Less frequent	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.

Health care providers 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.

4.9 Overdose

Symptoms

Symptoms of overdosage may be any of those listed under section 4.8 above and in these cases the dosage should be reduced or the medicine discontinued.

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.20.2.3. Tuberculostatics.

Pharmacotherapeutic group: Antimycobacterial (drugs for treatment of tuberculosis). ATC code: J04AK02

Mechanism of action

Ethambutol is bacteriostatic. It is effective against *Mycobacterium tuberculosis* and *M. bovis* with a 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

Core:

Dibasic calcium phosphate

Gelatin

Magnesium stearate

Maize starch

Sorbitol

Coating:

Ethyl cellulose

Hydroxypropyl methylcellulose (E464)

Macrogol/PEG (E1521)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister in the outer carton until required for use.

6.5 Nature and contents of container

ETHAMBUTOL 400 mg PHARMA-Q tablets are packed in PVC-PVDC/Alu blister packs in a cardboard carton.

Pack size: 1 blister of 28 tablets or multiple blisters may be packed in a carton (24 blisters of 28 tablets).

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

57/20.2.3/0707

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 May 2025

10 DATE OF REVISION OF THE TEXT

Not applicable