Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ethambutol 400mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg Ethambutol Hydrochloride.

Excipients: Each tablet contains 130mg sucrose and 23mg sorbitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
Smooth, grey, biconvex, bevel-edged film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The primary treatment and re-treatment of tuberculosis and for prophylaxis in cases of inactive tuberculosis or large-tuberculin-positive reaction. Ethambutol should only be used in conjunction with other anti-tuberculous drugs to which the patient's organisms are susceptible.

4.2 Posology and method of administration

Route of administration: Oral

Posology:

Recommended Dosage

The dosage of ethambutol must be carefully calculated on the basis of individual body weight to minimise the risk of toxicity.

Adults:
The usual daily dosage is 15-25 mg/kg body weight given as a single dose.

Children:
The usual daily dosage is 20 (15-25) mg/kg body weight given as a single dose.

Higher doses may be required, this is to be handled on a case by case basis with specialists in the field.

Dosing in infants less than 3 months is not recommended due to lack of data in this population.

Renal Insufficiency

Dosage should be reduced in patients with renal dysfunction. The following guide may be used

GFR < 50	Dose mg/kg	Interval
> 25ml/minute	15 - 25	24 - 36 hrs
10 – 25	7.5 - 15	48 hrs
< 10 or on dialysis	5	48 hrs

This drug should not be used as a sole anti-tuberculosis agent, but should be given with at least one other anti-tuberculosis drug to avoid development of resistant strains.

Geriatric Use

Dose selection should be cautious, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.3 Contraindications

Known hypersensitivity to ethambutol or to any of the components of Ethambutol Tablets. It is also contra-indicated in patients with known optic neuritis, or retrobulbar neuritis, unless clinical judgement determines that it may be used.

Ethambutol is contra-indicated in patients who are unable to appreciate and report visual side-effects or changes in vision (e.g very young children, unconscious patients).

4.4 Special warnings and precautions for use

Ethambutol may produce decreases in visual acuity and colour vision, which may appear to be due to optic/retrobulbar neuritis. This effect may be related to dose and duration of treatment. This effect is generally reversible when administration of the drug is discontinued promptly. However, irreversible blindness has been reported.

Liver toxicities including fatalities have been reported. Baseline and periodic assessment of hepatic functions, should be performed.

Patients with decreased renal function may need to have the dosage adjusted as determined by blood levels of ethambutol.

As with any potent drug, baseline and periodic assessment of organ system functions, including renal, hepatic, and haematopoietic, should be performed.

Ethambutol may reduce the renal clearance of urates such as uric acid possibly leading to hyperuricemia. Acute attacks of gout have been reported.

Because this drug has a unique effect on the eye, it is recommended that patients undergo a full ophthalmic examination before starting treatment. This should include visual acuity, colour vision, perimetry and ophthalmoscopy. In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions. In such patients consideration should be given to the relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult.

The change may be unilateral or bilateral and hence both eyes must be tested individually.

Many physicians consider that routine ophthalmological examination for adults is not thereafter necessary, but patients should be informed of the importance of stopping ethambutol administration immediately if they experience any change in vision, and informing their physician. Routine ophthalmological examinations may be considered desirable when treating young children.

Ethambutol should be used in young children and those with language or communication difficulties, where appropriate, with advice concerning the need to report visual side-effects being given to parents or other family members.

This product should only be administered with great caution in patients with convulsive disorder.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids containing aluminium hydroxide have impaired the absorption of ethambutol.

Ethambutol may react with phentolamine to elicit a false-positive test for pheochromocytoma.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant or lactating women. Ethambutol has been reported to cross the placenta and is excreted into breast milk. There are reports of ophthalmic abnormalities occurring in infants born to women on antituberculous therapy that included ethambutol hydrochloride. Ethambutol hydrochloride should be used during pregnancy only if the benefit justifies the potential risk to the foetus.

4.7 Effects on ability to drive and use machines

Ethambutol may produce a unique type of visual impairment (see 4.8 Undesirable effects). Numbness and paraesthesia of the extremities have been reported. Therefore, patients should be cautioned about their ability to drive a car or operate hazardous machinery if they experience any of these symptoms.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Leukopenia, neutropenia, thrombocytopenia

Immune system disorders:

Hypersensitivity,anaphylactic/ anaphylactoid reactions (including shock and fatalities). Hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present.

Nervous system disorders:

Dizziness, hypoaesthesia, paraesthesia

Eye disorders:

Decreased visual acuity, optic neuropathy, optic neuritis, retrobulbar neuritis, visual field defect, colour blindness, scotoma, congenital ophthalmic abnormalities, blindness

Respiratory disorders, thoracic and mediastinal disorders:

Pulmonary infiltrates with or without eosinophilia

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea, anorexia

Hepatobiliary disorders:

Aspartate aminotransferase increased, alanine aminotransferase increased, liver toxicities including fatalities

S*kin and subcutaneous tissue disorders:*

Hypersensitivity, rash, pruritis, urticaria, Stevens-Johnson syndrome, photosensitive lichenoid eruptions, toxic epidermal necrolysis, bullous dermatitis

Renal and urinary disorders:

Gout, hyperuricemia, interstitial nephritis

General disorders and administration site reactions:

Fever

4.9 Overdose

No specific antidote, but gastric lavage should be employed if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ethambutol is bacteriostatic. It is effective against *Mycobacterium tuberculosis* and *M. bovis* with an MIC of 0.5 - 8 µg per ml. While it has activity against some atypical Mycobacteria including *M. kansasii,* activity against other micro-organisms 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

Ethambutol is readily absorbed after oral administration and this absorption is not significantly impaired by food. After a single dose of 25mg/kg body weight, within 4 hours peak plasma concentrations of up to 5µg/ml are obtained; by 24 hours the concentration decreases to less than 1µg/ml. Most of a dose is excreted unchanged in the urine and up to 20% in faeces, within 48 hours. From 8 - 15% of a dose appears in urine as inactive metabolites.

Ethambutol readily diffuses into red blood cells and into the cerebrospinal fluid when the meninges are inflamed. It has also been reported to cross the placenta.

5.3 Preclinical safety data

Ethambutol hydrochloride has been shown to be teratogenic in pregnant mice and rabbits when given in high doses. When pregnant mice or rabbits were treated with high doses of ethambutol hydrochloride, fetal mortality was slightly but not significantly (P>0.05) increased. Female rats treated with ethambutol hydrochloride displayed slight but insignificant (P>0.05) decreases in fertility and litter size.

In foetuses born of mice treated with high doses of ethambutol hydrochloride during pregnancy, a low incidence of cleft palate, exencephaly and abnormality of the vertebral column were observed. Minor abnormalities of the cervical vertebra were seen in the newborn of rats treated with high doses of ethambutol hydrochloride during pregnancy. Rabbits receiving high doses of ethambutol hydrochloride during pregnancy gave birth to two foetuses with monophthalmia, one with a shortened right forearm accompanied by bilateral wrist –joint contracture and one with hare lip and cleft palate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Gelatin
Sorbitol 70% (Non-crystallising)
Magnesium Stearate
Stearic Acid

Coating for Tablets

Polydextrose
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Iron oxide black (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene bottle with urea screw cap containing 56, 100 or 500 tablets.

or

Glass bottle with metal screw cap containing 56, 100 or 500 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/180/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1977

Date of last renewal: 1st April 2007

10 DATE OF REVISION OF THE TEXT

March 2015