SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ethambutol 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 100mg Ethambutol Hydrochloride.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.
Smooth, yellow, circular, biconvex film coated tablet, plain on both sides.

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-tuberculinpositive reaction. Ethambutol should only be used in conjunction with other anti-tuberculous drugs to which the patient's organisms are susceptible.
Consideration should be given to official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration

Route of administration:
Oral
Posology:

Recommended Dosage

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

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

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

Adults

For primary treatment and prophylaxis: Ethambutol should be administered in a single daily dose of 15mg/kg, concomitant drugs being maintained at their recommended dosage levels.

For re-treatment: For the first 60 days of treatment, ethambutol should be administered in a single daily dose of 25mg/kg. Thereafter the dosage should be reduced to 15mg/kg, concomitant drugs being maintained at their recommended dosage levels.

Children

For primary treatment and re-treatment: For the first 60 days of treatment, a single daily oral dose of 25mg/kg. Thereafter the dosage should be reduced to 15mg/kg, concomitant drugs being maintained at their recommended dosage levels.

For prophylaxis: A single daily oral dose of 15mg/kg, concomitant drugs being used at their recommended dosage levels

As children might be less likely or unable to report ocular toxicity, particular caution may be warranted (see section 4.4).

Elderly

As for adults. However, patients with decreased renal function may need to have the dosage adjusted as determined by blood levels of ethambutol.

4.3 Contraindications

Ethambutol is contraindicated in patients who are known to be hypersensitive to the active substance or any of the excipients.

Ethambutol is contraindicated in patients who have optic neuritis, or retrobulbar neuritis unless clinical judgement determines that the benefit outweighs the risk.

4.4 Special warnings and precautions for use

Renal function:

Toxic effects are more common if renal function is impaired.

Ocular toxicity:

Ethambutol may produce a unique type of visual impairment which is generally reversible and which appears to be due to optic neuritis and to be related to dose and duration of treatment.

Less than 1% of patients undergoing treatment with the higher dose regimen of 25mg/kg/day for two months, and 15mg/kg/day thereafter, have exhibited decrease in visual acuity. It is recommended that patients undergo a full ophthalmic examination before starting treatment. This should include visual acuity, colour vision, perimetry and ophthalmoscopy. Any change may be unilateral or bilateral and hence both eyes should be tested individually.

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.

Any negative effects on vision are generally reversible when administration of the drug is discontinued promptly and recovery of visual acuity has usually occurred over a period of weeks to months after the drug was discontinued. Patients have then received Ethambutol at lower dosages without toxicity.

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

Hepatic impairment:

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

Other warnings:

Consideration should be given to current clinical guidance on the appropriate use of antituberculous drugs.

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 medicinal products and other forms of interaction

Aluminium Hydroxide impairs the absorption of Ethambutol. Acid suppressing drugs or antacids that do not contain Aluminium Hydroxide should be used during Ethambutol therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of ethambutol in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Ethambutol is not recommended during pregnancy and in women of childbearing potential unless the potential benefit to the mother is considered to outweigh any possible risks.

Breast-feeding

Ethambutol/metabolites have been identified in breastfed newborns/infants of treated women. There is insufficient information on the effects of ethambutol in newborns/infants.

Breast-feeding is not recommended during Ethambutol treatment unless the benefit of breast-feeding to the child is considered to outweigh any possible risks.

4.7 Effects on ability to drive and use machines

Patients who suffer from visual impairment during treatment with ethambutol should not drive or operate machinery.

Numbness, paraesthesia, dizziness, disorientation are also among possible side effects that may affect a patient's ability to drive or operate machinery, if affected, patients should not drive or operate machinery.

4.8 Undesirable effects

In this section, frequencies of undesirable effects are defined as follows: Frequency: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000), very rare (<1/10,000).

Blood & lymphatic system disorders:
Rare: Thrombocytopenia
Very rare: Leucopenia, neutropenia

Immune system disorders:
Very rare: Hypersensitivity, anaphylactoid reactions, (see also Skin and subcutaneous tissue disorders)

Metabolic & nutrition disorders:
Uncommon: Hyperuricaemia
Very rare: Gout

Nervous system disorders:
Rare: Peripheral neuropathy, numbness, paraesthesia of the extremities
Very rare: headache, dizziness, disorientation

Psychiatric disorders:
Very rare: mental confusion, hallucinations

Eye disorders:
Uncommon: Optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain)

Respiratory, thoracic & mediastinal disorders:
Very rare: Pneumonitis, pulmonary infiltrates, with or without eosinophilia

Gastrointestinal disorders:
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.

Hepatobiliary disorders:
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.

Skin & subcutaneous tissue disorders:
Rare: Rash, pruritus, urticaria
Very rare: photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis
not known: drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)

Musculoskeletal and connective tissue disorders:
Very rare: Joint pains

Renal & urinary disorders:
Very rare: Interstitial nephritis

General disorders and administration site conditions:
Very rare: Malaise, pyrexia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

4.9 Overdose

Symptoms: Gastrointestinal disturbances, vomiting, fever, headache, anorexia, dizziness, hallucinations and/or visual disturbances.
Treatment: No specific antidote, but gastric lavage should be employed if necessary

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial , ATC code: J04AK02.

Mode of Action

Ethambutol is bacteriostatic. It is effective against *Mycobacterium tuberculosis* and *M. bovis* with an MIC of 0.5 - 8 μg per ml. the exact mechanisim of action is unknown.
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.

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
Ethambutol is readily absorbed after oral administration and this absorption is not significantly impaired by food.
Distribution
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. 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.
Metabolism and Excretion
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.

5.3 Preclinical safety data

Ethambutol hydrochloride had 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 (>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

Tablet core:
Sodium starch glycollate
Maize starch
Povidone
Colloidal anhydrous silica
Microcrystalline cellulose
Magnesium stearate

Film coating:
Opadry II 45F32810 Yellow.
Containing Polydextrose, hydroxypropylmethylcellulose, polyethylene glycol 4000, titanium dioxide (E171), iron oxide yellow (E172), and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C.
Store in original package to protect from moisture.
Keep out of reach and sight of children.

6.5 Nature and contents of container

HDPE bottles with HDPE/PP/EPE cap containing 56 tablets

6.6 Special precautions for disposal

No special precautions. Any unused product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Intrapharm Laboratories Limited,
The Courtyard Barns,

Choke Lane,
Cookham Dean,
Maidenhead,
Berkshire,
SL6 6PT,
UNITED KINGDOM.

8 MARKETING AUTHORISATION NUMBER(S)

PL 17509/0081

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 September 2010
Date of latest renewal: 6 September 2015

10 DATE OF REVISION OF THE TEXT

16/07/2024