Ethambutol 100mg and 400mg Tablets

PL 15760/0010-11

UKPAR

TABLE OF CONTENTS

Lay Summary ........................................... Page 2
Scientific discussion ................................. Page 3
Steps taken for assessment ......................... Page 12
Steps taken after authorisation – summary ...... Page 13
Summary of Product Characteristics
Product Information Leaflet
Labelling
Ethambutol 100mg and 400mg Tablets

On 7th September 2010, the MHRA granted Peckforton Pharmaceuticals Limited Marketing Authorisations (licences) for Ethambutol 100mg and 400mg Tablets (PL 15760/0010-11).

Ethambutol 100mg and 400mg Tablets contain the active ingredient, ethambutol hydrochloride. Ethambutol belongs to a group of medicines called antituberculosis drugs. Ethambutol 100mg and 400mg Tablets are used for the treatment and prevention of tuberculosis, an infectious disease affecting the lungs.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ethambutol 100mg and 400mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Ethambutol 100mg and 400mg Tablets

PL 15760/0010-11

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 8
Clinical assessment (including statistical assessment) Page 9
Overall conclusions and risk benefit assessment Page 11
INTRODUCTION

The UK granted Peckforton Pharmaceuticals Limited Marketing Authorisations for the medicinal products Ethambutol 100mg and 400mg Tablets (PL 15760/0010-11) on 7th September 2010. These prescription only medicines (POM) are indicated for the primary treatment and re-treatment of tuberculosis and for prophylaxis in cases of inactive tuberculosis or large-tuberculin positive reaction.

These applications for Ethambutol 100mg and 400mg Tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Myambutol 100mg and 400mg Film-Coated Tablets, first authorised in the UK to Genus Pharmaceuticals UK in 1st July 1999.

The products contain ethambutol hydrochloride, which is a bacteriostatic agent. It is mainly effective against Mycobacterium tuberculosis and M. bovis. Ethambutol is indicated for the primary treatment and re-treatment of tuberculosis and for prophylaxis in cases of inactive tuberculosis or large-tuberculin positive reaction.

The pharmacovigilance system as described by the applicant fulfils the requirements. It also provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

The Marketing Authorisation Holder has provided adequate justification for not submitting a risk management plan (RMP).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Ethambutol hydrochloride
INN: Ethambutol hydrochloride
Chemical name: (2S,2′S)-2,2′-(ethylenediimino)dibutan-1-ol dihydrochloride.

Structure:

Physical form: White crystalline powder.
Solubility: Freely soluble in water.
Soluble in alcohol and in methanol.
Slightly soluble in ether and in chloroform.

Molecular formula: \( \text{C}_{10}\text{H}_{26}\text{Cl}_{2}\text{N}_{2}\text{O}_{2} \)
Molecular weight: 277.23

Ethambutol hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredients.

An appropriate specification is provided for ethambutol hydrochloride, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing ethambutol hydrochloride to be a physically and chemically stable drug, and supporting an appropriate retest period.

DRUG PRODUCT
Other ingredients
Other ingredients in the tablet core consist of pharmaceutical excipients sodium starch glycollate, maize starch, povidone, colloidal anhydrous silica, microcrystalline cellulose and magnesium stearate.
Ingredients in the film-coating are: opadry II grey OY-GM-27600 (containing polydextrose, hydroxypropylmethylcellulose, polyethylene glycol 4000, titanium dioxide, iron oxide yellow, iron oxide black) and purified water.

All the ingredients with the exception of opadry II grey OY-GM-27600 comply with their relevant European Pharmacopoeia monographs. Opadry II grey OY-GM-27600 complies with in-house specifications.

With the exception of magnesium stearate, none of the excipients used contain material of animal or human origin. The applicant has provided a valid TSE Certificate of Suitability for magnesium stearate.

**Product development**
The objective of the development programme was to produce products that could be considered generic medicinal products of Myambutol 100mg and 400mg Film-Coated Tablets (Genus Pharmaceuticals UK).

The reference product used in the bioequivalence studies is Myambutol 400mg Film-Coated Tablets, authorised in Germany to Riemser Arzneimittel. The German product is considered qualitatively and quantitatively similar to the reference product.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative in vitro dissolution profiles and impurity profiles have been provided for the proposed and originator products.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on batch data and controls on the finished product. Process validation data on batches have been provided.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The product is packaged in:
1) Polypropylene bottles with child resistant polypropylene cap containing 56 tablets.
2) Clear polyvinyl chloride (PVC), polyethylene (PE), polyvinylidene (PVDC) and aluminium blister packs containing 60 tablets.

Specifications and Certificates of Analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 36 months has been set, with special storage
instructions ‘Store below 30°C’, ‘Store in original package to protect from moisture’ and ‘Keep out of reach and sight of children.’

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**
These are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.

**Patient Information Leaflet (PIL)**
These are pharmaceutically satisfactory.

**MAA Form**
These are pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Ethambutol 100mg and 400mg Tablets are submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Myambutol 100mg and 400mg Film-Coated Tablets, first authorised in the UK to Genus Pharmaceuticals UK in 1st July 1999.

No new preclinical data have been supplied with these applications and none are required for applications of this type.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the Marketing Authorisation Holder has included a single bioequivalence study:

A randomised, open label, balanced, two-treatment, two-period, crossover, single dose bioequivalence study comparing the pharmacokinetics of Ethambutol 400mg Tablets (Test) versus Myambutol 400mg Tablets (Reference) in healthy volunteers.

Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. There was a washout period of 13 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:
Geometric Least Mean Squares and 90% Confidence Interval

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters of Ethambutol hydrochloride</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-\infty} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol hydrochloride: Test</td>
<td>6397.85</td>
<td>6980.10</td>
<td>1028.52</td>
</tr>
<tr>
<td>Ethambutol hydrochloride: Reference</td>
<td>6300.45</td>
<td>6873.88</td>
<td>999.15</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>101.56</td>
<td>96.64 – 106.73</td>
<td>92.02 – 115.32</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for ethambutol hydrochloride within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.
DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Ethambutol 100mg and 400mg Tablets can be considered as generic medicinal products to the reference products Myambutol 100mg and 400mg Film-Coated Tablets.

The grant of Marketing Authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Ethambutol 100mg and 400mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Ethambutol 400mg Tablets and the reference product.

As the 400mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 400mg strength can be extrapolated to Ethambutol 100mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with ethambutol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
# STEPS TAKEN FOR ASSESSMENT

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 20(^{th}) March 2009.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 23(^{rd}) March 2009.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the clinical dossier on 15(^{th}) June 2009. Following assessment of the application, the MHRA requested further information relating to the quality dossier on, 28(^{th}) September 2009, 11(^{th}) May 2010 and 6(^{th}) July 2010.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 8(^{th}) April 2010 for the clinical section. The applicant responded to the MHRA’s requests, providing further information on 8(^{th}) April 2010, 2(^{nd}) June 2010 and 15(^{th}) July 2010 for the quality section.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 7(^{th}) September 2010.</td>
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</tbody>
</table>
Ethambutol 100mg and 400mg Tablets

PL 15760/0010-11

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Ethambutol 100 mg and 400 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
PL 15760/0010: Each film coated tablet contains 100mg Ethambutol Hydrochloride.
PL 15760/0011: Each film coated tablet contains 400mg Ethambutol Hydrochloride.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Film coated tablet.
Smooth, grey, 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-tuberculin positive 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
Ocular Toxicity
Ethambutol causes ocular toxicity and patients should be advised to report any changes of visual acuity. Visual acuity should be examined prior to the start of therapy and should be monitored every four weeks during treatment. For patients with pre-existing visual defects or renal insufficiency the frequency of tests should be increased to every second week or more, depending on clinical assessment. Each eye should be tested separately as ocular toxicity can be unilateral or bi-lateral. Ophthalmologic examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy.

Patients who are unable to report their visual acuity should be more closely monitored for any signs of deterioration during treatment with Ethambutol. 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. Ethambutol therapy should be stopped immediately if visual disturbances are observed (see section 4.8).

Renal Impairment
Renal function should be checked before treatment with antituberculous drugs and appropriate dosage adjustments made. Ethambutol should preferably be avoided in patients with renal impairment, but if used the dose should be reduced and the plasma-drug concentration monitored. Toxic effects are more common if renal function is impaired.

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 PREGNANCY AND LACTATION
There are no adequate and well-controlled studies in pregnant or lactating women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Ethambutol should not be used in pregnant women, women of childbearing potential or lactating women unless the potential benefit to the mother is considered to outweigh any possible risks.

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
The most important adverse effect resulting from Ethambutol use is retrobulbar neuritis with a reduction in visual acuity.

The adverse event data below contains all reactions that are considered at least possibly related to Ethambutol and is based on data collected, mainly from published literature collected post authorisation. The undesirable effects have been arranged by body system, organ class and absolute frequency, and are defined using the following convention:
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); not known (cannot be estimated from the available data).

Nervous system disorders:
Common: visual disturbances caused by optic neuritis (retrobulbar neuritis). This effect is thought to be dose related and frequency is dependent on both dose and duration of treatment. It occurs most frequently with doses of 25 mg/kg body weight and after two months of therapy, however optic neuritis has also occurred after only a few days of therapy. The effect is often reversible upon discontinuation of therapy. To avoid permanent damage visual acuity should be checked regularly during treatment and therapy discontinued immediately when visual disturbances occur. 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. Not known: peripheral neuritis, paraesthesia (especially in legs), numbness, burning pain, weakness (hands and feet), dizziness, headache, tremor.
Psychiatric disorders:
*Not known:* confusion, disorientation, hallucination.

Gastrointestinal disorders:
*Not known:* metallic taste, nausea, vomiting, anorexia, flatulence, abdominal pain, loss of appetite, upset stomach.

Hepatobiliary disorders:
*Not known:* jaundice, transient increase in liver enzymes.

Renal and urinary disorders:
*Not known:* nephrotoxicity including interstitial neuritis.

General disorders and administration site conditions:
*Not known:* fever.

Immune system disorders
*Not known:* hypersensitivity, allergic reactions, anaphylaxis, allergic pneumonitis

Skin & subcutaneous tissue disorders
*Not known:* Rash, pruritus, urticaria, photosensitive lichenoid eruptions, bullous dermatitis, Stevens Johnson syndrome, epidermal necrolysis

Blood and lymphatic system disorders:
*Not known:* thrombocytopenia, leukopenia, neutropenia, eosinophilia.

Metabolism and nutrition disorders
*Very common:* hyperuricaemia,
*Not known:* gout.

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 mechanism 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 grey OY-GM-27600 (containing polydextrose, hydroxypropylmethylcellulose, polyethylene glycol 4000, titanium dioxide, iron oxide yellow, iron oxide black)
- 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
Polypropylene bottles with child resistant polypropylene cap containing 56 tablets.
Clear PVC/PE/PVDC and aluminium blister pack containing 60 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
Peckforton Pharmaceuticals Ltd,
Crewe Hall,
Crewe,
Cheshire,
CW1 6UL.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15760/0010-11
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/09/2010

10 DATE OF REVISION OF THE TEXT
07/09/2010
**PATIENT INFORMATION LEAFLET**

**ETHAMBUTOL 400 mg TABLETS**
(Ethambutol Hydrochloride)

**Read all of this leaflet carefully before you start taking this medicine.**
Keep this leaflet. You may need to read it again. If you have any further questions ask your doctor or pharmacist. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours. If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**
1. What Ethambutol Tablets are and what they are used for
2. Before you take Ethambutol Tablets
3. How to take Ethambutol Tablets
4. Possible side effects
5. How to store Ethambutol Tablets
6. Further information

**1. WHAT ETHAMBUTOL TABLETS ARE AND WHAT THEY ARE USED FOR**
The name of your medicine is Ethambutol Tablets. Ethambutol belongs to a group of medicines called antituberculosis drugs and is used for the treatment and prevention of tuberculosis, an infectious disease mainly affecting the lungs.

**2. BEFORE YOU TAKE ETHAMBUTOL TABLETS**

**Do not take Ethambutol Tablets:**
- if you have sight problems caused by inflammation of nerves in your eye (optic neuritis).
- if you are allergic (hypersensitive) to ethambutol hydrochloride or to any of the other ingredients (see list under ‘What Ethambutol Tablets contain’ in Section 6).

**Problems with your sight**
You should have your eyesight checked before taking these tablets. If you notice any changes to your vision whilst taking these tablets, you should stop taking them and notify your doctor immediately. Very young children or patients with communication difficulties should be closely monitored for any signs of sight problems by their parents or carers.

**Taking other medicines**
You should not take ethambutol tablets at the same time as antacid medicine containing aluminium hydroxide (used to treat heartburn and indigestion) as this can make ethambutol less effective.

Please tell your doctor or pharmacist if you are taking or have recently take any other medicines, including medicines obtained without a prescription.

**Pregnancy and breast-feeding**
You should not take this medicine if you are pregnant, breast-feeding or trying for a baby without consulting your doctor first.

**Driving and using machines**
Ethambutol occasionally causes sight problems and tingling or numbness in hand or feet. After taking this medicine you should not drive or use machinery, until you know how it affects you.
3. HOW TO TAKE ETHAMBUTOL TABLETS
Always take Ethambutol Tablets exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.
The dosage of ethambutol varies from person to person depending on your age, how much you weigh and whether it is being used for the treatment or for the prevention of tuberculosis.
Elderly patients who have kidney problems may need blood tests so that their doctor can reduce the dose in some cases.
Ethambutol Tablets should be taken once per day. They should be swallowed whole with a drink of water; do not chew or crush the tablets.
If you are not sure how many tablets to take, or when to take them, ask your pharmacist.
Keep taking your tablets for as long as your doctor directed, even if you feel better.

Adults:
**Prevention and first time treatment:** The usual dose of ethambutol for adults for prevention of tuberculosis or for first time treatment of tuberculosis is 15mg per kg of body weight per day.

**Second time (or subsequent) treatment:** The usual dose of ethambutol for adults for second time (or subsequent) treatment of tuberculosis is 25mg per kg of body weight per day for the first 60 days, reducing to 15mg per kg of body weight per day for as long as the doctor considers necessary.

Children:
**Prevention:** The usual dose of ethambutol for children for prevention of tuberculosis is 15mg per kg of body weight per day.

**First, second time (or subsequent) treatment:** The usual dose of ethambutol for children for treatment of tuberculosis is 25mg per kg of body weight per day for the first 60 days, reducing to 15mg per kg of body weight per day for as long as the doctor considers necessary.
If you take more Ethambutol Tablets than you should
If you have taken an overdose of Ethambutol Tablets (that is more than the doctor has told you to) get medical help immediately, either by calling your doctor or going to the nearest hospital casualty department. Remember to take the labelled medicine bottle with you, whether there are any Ethambutol Tablets left or not.

If you forget to take Ethambutol Tablets
If you forget to take a tablet you should take it as soon as you remember. However, if this is within 2 hours of your next dose you should skip the missed tablet and carry on taking the rest of your tablets as usual. Do not take a double dose to make up for a forgotten tablet.

4. POSSIBLE SIDE-EFFECTS
Like all medicines, ethambutol can cause side-effects although not everybody gets them.

The following side-effects may be serious.

- A severe allergic reaction, signs of which are, difficulty in breathing, wheezing, a flushed appearance, agitation or an irregular heartbeat. **If this occurs, stop taking this medicine and contact your doctor immediately.**
- Sight problems including colour blindness. In the majority of cases these will return to normal after stopping treatment. However in rare circumstances, the problem may take longer to heal or become permanent. **If you notice any changes or problems with your sight, contact your doctor immediately.**
- Kidney problems. If you have pain in your lower back, pain, burning or difficulty when you pass urine or blood in your urine you should **contact your doctor as soon as possible.**

Other possible side effects are:

- Allergic reactions including skin rash and itching
- Breathing problems
- Reduction in certain types of blood cells which may cause an increased risk of infection
- Dizziness, confusion, disorientation, headache hallucination
- Gut and stomach problems such as loss of appetite, feeling or being sick, diarrhoea, metallic taste, weight loss, wind or stomach pain
- Severe skin conditions with blistering of the skin, mouth, eyelids and genitals or peeling skin
- Numbness; pins and needles, weakness, burning pain, shaking
- Gout, signs of which are, pain or swelling in your joints (especially big toe) with tender hot skin over affected joints
- Skin problems including hard lumps or red patches often on the backs of arms and hands
- Reduced blood platelets which can cause a purple rash, prolonged bleeding after injury or bruising easily
- Liver problems which may result in pale stools, dark urine, or make your skin or eyes look slightly yellow
- Abnormal blood test results for liver function or urea concentration

If any of the side-effects get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE ETHAMBUTOL TABLETS

*Keep out of the reach and sight of children.*

Do not use Ethambutol Tablets after the expiry date which is stated on the packaging after EXP.

Store below 30°C in the original packaging to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

**What Ethambutol Tablets Contain:**

The active ingredient is ethambutol (as ethambutol hydrochloride). Each tablet contains 400mg of ethambutol.

Other ingredients are:

- Tablet core: Microcrystalline cellulose, sodium starch glycolate, maize starch, povidone, colloidal anhydrous silica and magnesium stearate.
- Tablet coating: Polydextrose, hydroxypropylmethylcellulose, polyethylene glycol 4000, purified water, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide black (E172)

**What Ethambutol Tablets look like and contents of the pack:**

Ethambutol 400mg Tablets are round grey coated tablets, plain on both sides. The tablets are available in bottles of 56 tablets or blister packs of 60 tablets (not all pack sizes may be marketed).

**Marketing Authorisation Holder and Manufacturer:**

Peckforton Pharmaceuticals Ltd., Crewe Hall, Crewe, Cheshire, CW1 6UL, England.

This leaflet was last approved in 08/2010
PATIENT INFORMATION LEAFLET

ETHAMBUTOL 100 mg TABLETS
(Ethambutol Hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again. If you have any further questions ask your doctor or pharmacist. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours. If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ethambutol Tablets are and what they are used for
2. Before you take Ethambutol Tablets
3. How to take Ethambutol Tablets
4. Possible side effects
5. How to store Ethambutol Tablets
6. Further information

1. WHAT ETHAMBUTOL TABLETS ARE AND WHAT THEY ARE USED FOR
The name of your medicine is Ethambutol Tablets. Ethambutol belongs to a group of medicines called antituberculosis drugs and is used for the treatment and prevention of tuberculosis, an infectious disease mainly affecting the lungs.

2. BEFORE YOU TAKE ETHAMBUTOL TABLETS
Do not take Ethambutol Tablets:
· if you have sight problems caused by inflammation of nerves in your eye (optic neuritis).
· if you are allergic (hypersensitive) to ethambutol hydrochloride or to any of the other ingredients (see list under ‘What Ethambutol Tablets contain’ in Section 6).

Problems with your sight
You should have your eyesight checked before taking these tablets. If you notice any changes to your vision whilst taking these tablets, you should stop taking them and notify your doctor immediately.
Very young children or patients with communication difficulties should be closely monitored for any signs of sight problems by their parents or carers.

Taking other medicines
You should not take ethambutol tablets at the same time as antacid medicine containing aluminium hydroxide (used to treat heartburn and indigestion) as this can make ethambutol less effective.
Please tell your doctor or pharmacist if you are taking or have recently take any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
You should not take this medicine if you are pregnant, breast-feeding or trying for a baby without consulting your doctor first.

Driving and using machines
Ethambutol occasionally causes sight problems and tingling or numbness in hand or feet. After taking this medicine you should not drive or use machinery, until you know how it affects you.
3. HOW TO TAKE ETHAMBUTOL TABLETS
Always take Ethambutol Tablets exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.
The dosage of ethambutol varies from person to person depending on your age, how much you weigh and whether it is being used for the treatment or for the prevention of tuberculosis.
Elderly patients who have kidney problems may need blood tests so that their doctor can reduce the dose in some cases.
Ethambutol Tablets should be taken once per day. They should be swallowed whole with a drink of water; do not chew or crush the tablets.
If you are not sure how many tablets to take, or when to take them, ask your pharmacist.
Keep taking your tablets for as long as your doctor directed, even if you feel better.

Adults:
**Prevention and first time treatment:** The usual dose of ethambutol for adults for prevention of tuberculosis or for first time treatment of tuberculosis is 15mg per kg of body weight per day.

**Second time (or subsequent) treatment:** The usual dose of ethambutol for adults for second time (or subsequent) treatment of tuberculosis is 25mg per kg of body weight per day for the first 60 days, reducing to 15mg per kg of body weight per day for as long as the doctor considers necessary.

Children:
**Prevention:** The usual dose of ethambutol for children for prevention of tuberculosis is 15mg per kg of body weight per day.

**First, second time (or subsequent) treatment:** The usual dose of ethambutol for children for treatment of tuberculosis is 25mg per kg of body weight per day for the first 60 days, reducing to 15mg per kg of body weight per day for as long as the doctor considers necessary.
If you take more Ethambutol Tablets than you should
If you have taken an overdose of Ethambutol Tablets (that is more than the doctor has told you to) get medical help immediately, either by calling your doctor or going to the nearest hospital casualty department. Remember to take the labelled medicine bottle with you, whether there are any Ethambutol Tablets left or not.

If you forget to take Ethambutol Tablets
If you forget to take a tablet you should take it as soon as you remember. However, if this is within 2 hours of your next dose you should skip the missed tablet and carry on taking the rest of your tablets as usual. Do not take a double dose to make up for a forgotten tablet.

4. POSSIBLE SIDE-EFFECTS
Like all medicines, ethambutol can cause side-effects although not everybody gets them.

The following side-effects may be serious.
- A severe allergic reaction, signs of which are, difficulty in breathing, wheezing, a flushed appearance, agitation or an irregular heartbeat. **If this occurs, stop taking this medicine and contact your doctor immediately.**
- Sight problems including colour blindness. In the majority of cases these will return to normal after stopping treatment. However in rare circumstances, the problem may take longer to heal or become permanent. **If you notice any changes or problems with your sight, contact your doctor immediately.**
- Kidney problems. If you have pain in your lower back, pain, burning or difficulty when you pass urine or blood in your urine you should **contact your doctor as soon as possible.**

Other possible side effects are:
- Allergic reactions including skin rash and itching
- Breathing problems
- Reduction in certain types of blood cells which may cause an increased risk of infection
- Dizziness, confusion, disorientation, headache hallucination
- Gut and stomach problems such as loss of appetite, feeling or being sick, diarrhoea, metallic taste, weight loss, wind or stomach pain
- Severe skin conditions with blistering of the skin, mouth, eyelids and genitals or peeling skin
- Numbness; pins and needles, weakness, burning pain, shaking
- Gout, signs of which are, pain or swelling in your joints (especially big toe) with tender hot skin over effected joints
- Skin problems including hard lumps or red patches often on the backs of arms and hands
- Reduced blood platelets which can cause a purple rash, prolonged bleeding after injury or bruising easily
- Liver problems which may result in pale stools, dark urine, or make your skin or eyes look slightly yellow
- Abnormal blood test results for liver function or urea concentration

If any of the side-effects get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE ETHAMBUTOL TABLETS
Keep out of the reach and sight of children.
Do not use Ethambutol Tablets after the expiry date which is stated on the packaging after EXP.
Store below 30ºC in the original packaging to protect from moisture.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION
What Ethambutol Tablets Contain:
The active ingredient is ethambutol (as ethambutol hydrochloride). Each tablet contains 100mg of ethambutol.

Other ingredients are:
Tablet core: Microcrystalline cellulose, sodium starch glycolate, maize starch, povidone, colloidal anhydrous silica and magnesium stearate.
Tablet coating: Polydextrose, hydroxypropylmethylcellulose, polyethylene glycol 4000, purified water, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide black (E172).

What Ethambutol Tablets look like and contents of the pack:
Ethambutol 100mg Tablets are round grey coated tablets, plain on both sides. The tablets are available in bottles of 56 tablets or blister packs of 60 tablets (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer:
Peckforton Pharmaceuticals Ltd., Crewe Hall, Crewe, Cheshire, CW1 6UL, England.
This leaflet was last approved in 08/2010
UKPAR Ethambutol 100mg and 400mg Tablets

PL 15760/0010

MA Holder: Peckforton Pharmaceuticals
Crewe Hall, Crewe, Cheshire, CW1 6UL

Attach dispensing label here

Barcode

Oral Use. Use as directed by your doctor.
Read the package leaflet before use.
Store below 30°C.
Keep in original package to protect from moisture.

Keep out of the reach and sight of children

Ethambutol 100mg Tablets

Each Tablet contains 100mg Ethambutol (as Ethambutol Hydrochloride)

56 Tablets

Ethambutol 100mg Tablets

Each Tablet contains 100mg Ethambutol (as Ethambutol Hydrochloride)

56 Tablets

Peckforton

Peckforton

Peckforton

Peckforton

Ethambutol 100mg Tablets

Each Tablet contains 100mg Ethambutol (as Ethambutol Hydrochloride)

Oral Use. Use as directed by your doctor. Read the package leaflet before use. Keep in original package to protect from moisture. Store below 30°C.

Batch:
Manuf:
Exp:
Ethambutol 100mg Tablets
Each Tablet contains 100mg Ethambutol (as Ethambutol Hydrochloride)
60 Tablets

Peckforton

Ethambutol 100mg Tablets
Each Tablet contains 100mg Ethambutol (as Ethambutol Hydrochloride)
60 Tablets

Peckforton

Oral Use.
Use as directed by your doctor.
Read the package leaflet before use.
Store below 30°C
Keep in original package to protect from moisture.

Keep out of the reach and sight of children

PL 15760/0010
Peckforton Pharmaceuticals Ltd
Crewe Hall, Crewe, Cheshire, CW1 8UL

Ethambutol 100mg Tablet
Peckforton Pharmaceuticals Ltd.
Ethambutol 400mg Tablets

Each Tablet contains 400mg Ethambutol (as Ethambutol Hydrochloride)

60 Tablets

Oral Use. Use as directed by your doctor. Read the package leaflet before use. Keep in original package to protect from moisture.
Store below 30°C.

MA Holder: Peckforton Pharmaceuticals Ltd
Crewe Hall, Crewe, Cheshire, CW1 6UL
PL 15760/0011

Batch: Manf: Exp:

Keep out of the reach and sight of children

POM

Barcode

Attach dispensing label here
**UKPAR Ethambutol 100mg and 400mg Tablets**

**PL 15760/0010-11**

**PL 15760/0011**

**MA Holder:** Peckforton Pharmaceuticals
Crewe Hall, Crewe, Cheshire, CW1 6UL

Attach dispensing label here

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**Oral Use.**

Use as directed by your doctor.

Read the package leaflet before use.

Store below 30°C.

Keep in original package to protect from moisture.

Keep out of the reach and sight of children

**Ethambutol 400mg Tablets**

Each Tablet contains 400mg Ethambutol (as Ethambutol Hydrochloride)

56 Tablets

**Ethambutol 400mg Tablets**

Each Tablet contains 400mg Ethambutol (as Ethambutol Hydrochloride)

56 Tablets