Public Assessment Report

Decentralised Procedure

Ethambutol 100mg & 400mg film-coated tablets

(ethambutol hydrochloride)

UK/H/2509/01-02/DC
UK licence number: PL 20117/0159-60

Morningside Healthcare Ltd
Lay Summary

On 27th July 2010, the MHRA granted Morningside Healthcare Ltd Marketing Authorisations (licences) for the medicinal products Ethambutol 100mg and 400mg film-coated tablets (PL 20117/0159-60, UK/H/2509/01-02/DC). These are prescription-only medicines (POM).

Ethambutol is an antibiotic (antibacterial medicine) used to treat infections. It belongs to a group of antibiotics called anti-tuberculosis drugs and is used in combination with other anti-tuberculosis agents to treat and prevent tuberculosis (TB), an infectious disease mainly affecting the lungs.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Ethambutol 100mg and 400mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

Information about Initial Procedure

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Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Ethambutol 100mg and 400mg film-coated tablets (PL 20117/0159-60) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Ethambutol 100mg Film-coated Tablets
Ethambutol 400mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Ethambutol hydrochloride 100 / 400 mg
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Grey, circular biconvex film coated tablets, 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-tuberculosis drugs to which the patient’s organisms are susceptible.

Before prescribing Ethambutol Tablets, consideration should be given to national and/or local guidance on the appropriate use of anti-bacterial agents

4.2 Posology and method of administration

Route of administration: Oral

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

Adults
For primary treatment and prophylaxis:
Ethambutol should be administered in a single daily oral 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 oral 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.

Elderly
As for adults. However, patients with decreased renal function may need to have the dosage adjusted as determined by blood levels of ethambutol.
In order to obtain maximum effect due to high serum levels, drug administration should be once daily.

4.3 Contraindications
Ethambutol is contra-indicated in patients who are known to be hypersensitive to the drug or to any of the excipients. It is also contra-indicated in patients with known optic neuritis unless clinical judgement determines that it may be used.

4.4 Special warnings and precautions for use
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.

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. Many physicians consider that routine ophthalmological examination for adults is not thereafter necessary, but patients should be informed the importance of reporting any change in vision. However, routine ophthalmological examinations may be considered desirable when treating young children.

4.5 Interaction with other medicinal products and other forms of interaction
No specific interaction studies have been carried out with ethambutol.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of ethambutol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lactation
Ethambutol should not be used in pregnant women or women of childbearing potential unless the potential benefit to the mother is considered to outweigh any possible risk to the foetus.

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.

4.8 Undesirable effects
Modern clinical data required to determine the frequency of undesirable effects are lacking for ethambutol. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

Blood & lymphatic disorders
Thrombocytopaenia, leucopenia, neutropenia, eosinophilia

Immune system disorders
Hypersensitivity, anaphylactoid reactions, (see also Skin & subcutaneous tissue disorders)

Metabolic & nutrition disorder
Hyperuricaemia, gout

Psychiatric disorders
Mental confusion, disorientation, hallucination.

Nervous system & psychiatric disorders
Peripheral neuropathy, numbness, paraesthesia of the extremities, dizziness, headache

Eye disorders
Optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain
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. The change may be unilateral or bilateral and hence both eyes must be tested individually. The effects are generally reversible when administration of the drug is discontinued promptly. In rare cases recovery may be delayed for up to one year or more and the effect may possibly be irreversible in these cases.

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 dosages without toxicity.

**Respiratory, thoracic and mediastinal disorders**

Pneumonitis, pulmonary infiltrates, with or without eosinophilia

**Gastrointestinal disorders**

Gastrointestinal disturbances 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 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**

Rash, pruritus, urticaria, photosensitive lichenoid eruptions, bullous dermatitis, Stevens Johnson syndrome, epidermal necrolysis

**Renal & urinary disorders**

Interstitial nephritis

**Other:**

Malaise, joint pains, pyrexia

**4.9 Overdose**

**Symptoms**

The overdosage symptoms include nausea, abdominal pain, fever, mental confusion, visual hallucinations, and optic neuropathy (retrobulbar neuritis)

**Treatment**

There is no specific antidote, but gastric lavage should be employed if necessary.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antimycobacterial

ATC Code for Ethambutol hydrochloride: J04AK02

**Mechanism of action:**

Ethambutol is bacteriostatic.

**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.

**Spectrum of antibacterial activity:**

Ethambutol 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. Kansarii*, activity against other micro-organisms has not yet been reported.

It is effective against tubercle bacilli resistant to other tuberculostatics.
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 5 μg/ml are obtained, by 24 hours the concentration decreases to less than 1 μg/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

Toxicologically studies in dogs on high prolonged doses produced evidence of myocardial damage and failure, and depigmentation of the tapetum lucidum of the eyes, the significance of which is not known. Degenerative changes in the central nervous system, apparently not dose-related, have also been noted in dogs receiving ethambutol hydrochloride over a prolonged period. In the rhesus monkey, neurological signs appeared after treatment with high doses given daily over a period of several months. These were correlated with specific serum levels of ethambutol and with definite neuroanatomical changes in the central nervous system. Focal interstitial carditis was also noted in monkeys which received ethambutol hydrochloride in high doses for a prolonged period.

Conflicting results are available on genotoxicity (negative Ames test, negative in human lymphocyte cell cultures, positive in mouse micronucleus). In mice, ethambutol administered together with sodium nitrite gave rise to an increased frequency of lymphomas and lung tumours, while ethambutol alone did not cause any increase in tumour frequency.

Cleft palate, exencephaly and vertebral column abnormalities have been observed with high doses in studies of reproduction toxicity in mice. Studies in rats and rabbits have shown that ethambutol in high doses causes minor abnormalities of the cervical vertebrae and monophthalmica, limb reduction defects, hare lip and cleft palate in the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Tablet:
Cellulose Microcrystalline, Maize Starch, Microcrystalline Cellulose, Povidone, Silica Colloidal anhydrous, Sodium Starch glycolate.

Film Coating:
Opadry II OY-GM-27600 containing
Hypermellose 15Cp, Iron oxide Black (E172), Iron oxide Yellow (E172), Polydextrose, Polyethylene glycol 4000, Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25oC. Any unused product or waste material should be disposed of in accordance with local requirements.

6.5 Nature and contents of container

Al/PVC blister. Pack sizes of 10, 14, 20, 28, 30, 56, 60, 84, 90 and 112 tablets are available
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements
7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Ltd
115 Narborough Road
Leicester.
LE3 0PA
U.K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0159
PL 20117/0160

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/07/2010

10 DATE OF REVISION OF THE TEXT
27/07/2010
Module 3
Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ethambutol 100mg and 400mg Film-coated 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 gets 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

Ethambutol is an antibiotic (antibacterial medicine) for treating infections. It belongs to a group of antibiotics called antituberculosis drugs and is used in combination with other antituberculosis agents to treat and prevent tuberculosis (TB), an infectious disease mainly affecting the lungs.

2. BEFORE YOU TAKE ETHAMBUTOL TABLETS

Do not take Ethambutol Tablets
- if you are allergic (hypersensitive) to ethambutol hydrochloride or any of the other ingredients of Ethambutol Tablets (See "Ingredients")
- if you have poor vision or swelling of the optic nerve which results in blurring of vision (optic neuritis)

Take special care with Ethambutol Tablets
- if you have been treated for kidney problems

Before treatment with Ethambutol Tablets your doctor may send you for an eye test and if you notice any changes to your vision during your treatment you should immediately let your doctor know.

Taking other medicines
It is not known if Ethambutol Tablets interacts with other medicines. However, it is best to tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Ethambutol Tablets with food and drink
Ethambutol Tablets may be taken with or without food.

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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ethambutol Tablets may cause visual disturbances that can impair your ability to drive and use machines.

3. HOW TO TAKE ETHAMBUTOL TABLETS

Always take Ethambutol Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dose of Ethambutol Tablets will be decided by your doctor based on your age, body weight and whether it is being used for the treatment or prevention of tuberculosis. Elderly patients who have kidney problems may need blood tests so their doctor can prescribe them an appropriate dose.

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

Re-treatment:
The usual dose of ethambutol for adults in the re-treatment of tuberculosis is 25mg per kg of body weight per day for the first 60 days and then reducing to 15mg per kg of body weight per day for as long as the doctor considers it necessary.

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

Treatment:
The usual dose of ethambutol for children for the treatment of tuberculosis is 25mg per kg of body weight per day for the first 60 days and then reducing to 15mg per kg of body weight per day for as long as the doctor considers it necessary.

Ethambutol Tablets will always be taken in combination with other antituberculosis medication; please make sure to follow the instructions within the supplied package leaflet(s).

If you take more Ethambutol Tablets than you should
If you have taken too many tablets or if someone accidentally swallows some, immediately contact your doctor, health care provider or the nearest hospital emergency department for further advice.
If you forget to take Ethambutol Tablets

If you miss a dose, just carry on with the next one as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking Ethambutol Tablets

Keep taking the medicine for as long as your doctor has told you, even if you are feeling better. If you stop the medicine too soon, your infection may not be completely cured. You should not stop treatment unless your doctor or healthcare provider tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ethambutol can cause side effects, although not everybody gets them.

Very rarely you may experience a serious allergic reaction known as an anaphylactic reaction which causes difficulty in breathing or irregular heartbeats.

If you experience any of the above then stop taking the tablets straight away and tell your doctor immediately.

The following side effects have been reported in patients treated with ethambutol. However, frequency estimates for these effects are not available:

- Changes in white blood cell count, reduction in blood platelets, which increases risk of bleeding or bruising,
- Abnormal liver function, hepatitis and yellowing of the skin or eyes (jaundice)
- Loss of appetite, nausea, vomiting, diarrhoea
- Tingling or numbness in the hands or feet, muscle weakness and wasting, dizziness, headaches
- Hypersensitivity, rash, itching, red patches often on the back of arms and hands, and blisters or peeling. Increased sensitivity to sunlight
- High levels of uric acid in the blood, gout
- Mental confusion, disorientation, hallucination
- Inflammation of the lungs
- General feeling of unwell, joint pain, fever
- Inflammation of the kidneys which can cause swollen ankles or high blood pressure

The most commonly reported serious side effects are visual changes due to inflammation of the optic nerve (optic neuritis). The frequency depends on the dose and duration of therapy. Typical initial signs include impairment of colour vision (red-green blindness) and constriction of visual field (central or peripheral scotoma). These changes are often reversible after discontinuation of treatment with ethambutol. If you notice any visual disturbance, please inform your doctor or healthcare provider immediately.

If any 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 carton and blister. The expiry date refers to the last day of that month.

Do not store above 25°C.

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

6. FURTHER INFORMATION

What Ethambutol Tablets contains

- The active substance is ethambutol hydrochloride. Each tablet contains either 100mg or 400mg of ethambutol hydrochloride.
- The other ingredients are

Core Tablet:

Cellulose Microcrystalline, Maize Starch, Microcrystalline Cellulose, Povidone, Silica Colloidal anhydrous, Sodium Starch glycolate.

Film Coating:

Opadry II CY-GM-27600 containing Hypermellose 15cP, Iron oxide Black (E172), Iron oxide Yellow (E172), Polydextrose, Polyethylene glycol 4000, Titanium Dioxide

What Ethambutol Tablets look like and contents of the pack

The tablets are grey, circular biconvex film-coated tablets, plain on both sides. The tablets are supplied in blister packs of 10, 14, 20, 28, 30, 56, 60, 84, 90 and 112 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Morningside Healthcare Ltd
115 Narborough Road, Leicester.
LE3 0PA, U.K.

Site responsible for batch release

Morningside Pharmaceuticals Ltd
5 Pavilion Way, Loughborough,
LE11 5QW, U.K.

This leaflet was last approved in July 2010.
Module 4

Labelling

Ethambutol 100mg Tablets – PL 20117/0159

Carton – pack size 56

Braille

Ethambutol #100 mg Tablets
Ethambutol 400mg Tablets – PL 20117/0160

Carton – pack size 56

ETHAMBUTOL 400mg Film-coated Tablets

Each film-coated tablet contains 400mg of ethambutol hydrochloride.

DOSEAGE: To be taken as directed by doctor. For oral use. Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not store above 25°C.

Braille

Ethambutol 400 mg Tablets
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- Blister foil
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Morningside Healthcare Ltd Marketing Authorisations for the medicinal products Ethambutol 100mg and 400mg film-coated tablets (PL 20117/0159-60, UK/H/2509/01-02/DC) on 27th June 2010. The products are prescription-only medicines (POM).

These are abridged applications for Ethambutol 100mg and 400mg film-coated tablets, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the UK products, Ethambutol / Myambutol Tablets 100mg and Ethambutol / Myambutol Tablets 400mg respectively (PL 17225/0004 and 0005), which were authorised to Genus Pharmaceuticals Holdings Limited on 1st July 1999. The cross-referenced products were originally awarded default conversion licences in April 1972 to Cyanamid of Great Britain Limited (PL 00095/0002-3), and subsequently underwent Change of Ownership (CoA) procedures to the current Genus Pharmaceuticals Holdings Limited licences in July 1999. The reference, innovator products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Morningside Healthcare Ltd applied for Marketing Authorisations for Ethambutol 100mg and 400mg film-coated tablets in Ireland.

Ethambutol 100mg and 400mg film-coated tablets are indicated for 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-tuberculosis drugs to which the patient’s organisms are susceptible. Before prescribing ethambutol tablets, consideration should be given to national and / or local guidance on the appropriate use of antibacterial agents.

Ethambutol hydrochloride is an anti-mycobacterial agent, effective against microorganisms of the genus *Mycobacterium*, mainly *M. tuberculosis* and *M. bovis*. The exact mechanism of action is currently unknown but it appears to inhibit the synthesis of one or more metabolites, thus causing impairment of cell metabolism, arrest of multiplication, and cell death.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the single bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Ethambutol 400mg film-coated tablets, to that of the reference product, Myambutol Tablets 400mg (sourced from Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of
the competent authorities (MHRA, UK) as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.
### II. ABOUT THE PRODUCT

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<td>PL 20117/0159-60</td>
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<td>Name and address of the authorisation holder</td>
<td>Morningside Healthcare Ltd 115 Narborough Road Leicester. LE3 0PA U.K.</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Ethambutol hydrochloride

Nomenclature:

INN: Ethambutol hydrochloride
Chemical name: (2S,2'S)-2,2'-((ethylenediimino)dibutan-1-ol dihydrochloride

Structure:

Molecular formula: C_{10}H_{26}Cl_{2}N_{2}O_{2}
Molecular weight: 277.23 g/mol
CAS No: 1070-11-7
Physical form: White crystalline powder
Solubility: Freely soluble in water, soluble in alcohol and in methanol, slightly soluble in ether and in chloroform

The active substance, ethambutol hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. 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 Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. The primary packaging is low-density polyethylene (LDPE), transparent bags. These LDPE bags are sealed and packed within triple laminated aluminium bags which are placed into fibreboard drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary LDPE bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated by the active substance manufacturer for active substance stored in packaging representative of the proposed commercial packaging. Based on the data, a retest period of 5 years has been set, when the active is stored in a tightly sealed container. This is satisfactory.
MEDICINAL PRODUCT

Description and Composition
Ethambutol 100mg and 400mg film-coated tablets are presented as grey, circular, biconvex film-coated tablets with no markings. The tablets contain 100mg or 400mg of ethambutol hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely cellulose microcrystalline, maize starch, microcrystalline cellulose, povidone, silica colloidal anhydrous and sodium starch glycolate making up the tablet core; and hypromellose 15cP, iron oxide black (E172), iron oxide yellow (E172), polydextrose, polyethylene glycol 4000 and titanium dioxide (E171) constituting ‘Opadry II OY-GM-27600’ which makes up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of the film-coating, Opadry II OY-GM-27600, which complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. There are no materials of human or animal origin contained in, or used in the manufacturing process for, the proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to obtain medicinal products pharmaceutically and therapeutically equivalent to the innovators using standard, safe excipients.

Comparative dissolution data were provided for both strengths of the test and appropriate reference products. The dissolution profiles were satisfactory.

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. All in-process control limits were met.

Finished product specification
The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for the 100mg and 400mg strength finished products. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System

The finished products are licensed for marketing in polyvinylchloride (PVC) / aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 10, 14, 20, 28, 30, 56, 60, 84, 90 and 112 film-coated tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage instructions are ‘Do not store above 25°C. Any unused product or waste material should be disposed of in accordance with local requirements’.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Ethambutol 400mg film-coated tablets, to the reference product, Myambutol Tablets 400mg (sourced from Germany).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Ethambutol 100mg and 400mg film-coated tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of ethambutol hydrochloride, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal products, Ethambutol / Myambutol Tablets 100mg and 400mg (Genus Pharmaceuticals Holdings Limited).

There are no objections to approval of Ethambutol 100mg and 400mg film-coated tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Ethambutol 100mg and 400mg film-coated tablets are indicated for 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-tuberculosis drugs to which the patient’s organisms are susceptible. Before prescribing ethambutol tablets, consideration should be given to national and / or local guidance on the appropriate use of antibacterial agents.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of ethambutol hydrochloride is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of ethambutol hydrochloride is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Ethambutol 400mg film-coated tablets (test) and Myambutol Tablets 400mg, sourced from the German market (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products.

This was a balanced, randomised, open-label, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study conducted in 24 healthy adult human male subjects under fasting conditions. Following a supervised fast of at least 10 hours, a single dose of the investigational products was administered orally to each subject in each period. A
A satisfactory washout period of 13 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of ethambutol hydrochloride were detected by a validated LC-MS/MS analytical method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$.

**Results:**

23 subjects completed the study and their results were used in the statistical analysis. There were no serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$ ng/ml</th>
<th>$\text{AUC}_{0-t}$ ng/ml/h</th>
<th>$\text{AUC}_{0-\infty}$ ng/ml/h</th>
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<tr>
<td>Test</td>
<td>1028.52</td>
<td>6397.85</td>
<td>6980.10</td>
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<tr>
<td>Reference</td>
<td>999.15</td>
<td>6300.45</td>
<td>6873.88</td>
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<tr>
<td>Ratio (90% CI)</td>
<td>103.01% (92.02 – 115.32)</td>
<td>101.56% (96.34 – 107.06)</td>
<td>101.56% (96.64 – 106.73)</td>
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$C_{\text{max}}$: maximum plasma concentration
$\text{AUC}_{0-t}$: area under the plasma concentration-time curve from time zero to t hours
$\text{AUC}_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Ethambutol 100mg film-coated tablets. As Ethambutol 100mg and 400mg film-coated tablets meet the criteria 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 the 100mg tablets.

**Clinical efficacy**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of ethambutol hydrochloride is well-established from its extensive use in clinical practice.
Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of ethambutol hydrochloride is well-known.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those for the reference products and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and is satisfactory. The PIL user test report has been evaluated and is satisfactory.

Labelling
The labelling is satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS
For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal products, Ethambutol / Myambutol Tablets 100mg and 400mg (Genus Pharmaceuticals Holdings Limited).

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ethambutol 100mg and 400mg film-coated 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Ethambutol 400mg film-coated tablets, and the reference product, Myambutol Tablets 400mg.

As the proposed products, Ethambutol 100mg and 400mg film-coated tablets, meet the criteria 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 were extrapolated to the 100mg strength tablets.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are satisfactory and consistent with those for the reference products.

The PIL is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s products, Ethambutol 100mg and 400mg film-coated tablets, and their respective reference products, Ethambutol / Myambutol Tablets 100mg and 400mg (Genus Pharmaceuticals Holdings Limited), are interchangeable. Extensive clinical experience with ethambutol hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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