ETHAMBUTOL 100 MG TABLETS
ETHAMBUTOL 400 MG TABLETS
PL 08137/0171-2

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Neolab Limited Marketing Authorisations for the medicinal products Ethambutol 100 mg and 400 mg Tablets (PL 08137/0171-2) on 16 November 2012. The products are available on prescription from your doctor and are used to prevent tuberculosis which is an infectious disease mainly affecting the lungs.

The active ingredient, ethambutol (as ethambutol hydrochloride), belongs to a group of medicines called anti-tuberculosis drugs.

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

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Neolab Limited Marketing Authorisations for the medicinal products Ethambutol 100 mg and 400 mg Tablets (PL 08137/0171-2) on 16 November 2012. The products are prescription-only medicines used 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.

These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Myambutol/Ethambutol Tablets 100 mg and 400 mg (Genus Pharmaceuticals, UK), which were first authorised in the UK on 17 April 1972.

The active ingredient, ethambutol (as ethambutol hydrochloride) is an oral antimycobacterial agent, which is specifically effective against actively growing micro-organism of genus Mycobacterium including M. tuberculosis. Resistance to ethambutol emerges rapidly when the drug is used alone. Therefore ethambutol is always given in combination with other antituberculosis drug.

A single-dose bioequivalence study was submitted to support these applications, comparing the applicant’s test product Ethambutol tablets 400 mg with the reference product Myambutol tablets 400 mg (manufactured by Riemser Arzneimittel, Germany) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Ethambutol 100 mg and 400 mg Tablets outweigh the risks and Marketing Authorisations were granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Ethambutol hydrochloride
Chemical Name: \((2S,2'S)-(2,2'-(ethylenediimino)dibutan-1-ol dihydrochloride
Molecular Formula: C\(_{10}\)H\(_{26}\)Cl\(_2\)N\(_2\)O\(_2\)

Structure

Molecular mass: 277.23
Appearance: White crystalline powder
Solubility: Freely soluble in water, soluble in alcohol and in methanol and slightly soluble in ether and in chloroform.

Ethambutol hydrochloride is the subject of a European Pharmacopoeia 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 specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is 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 specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium starch glycolate, maize starch, povidone, colloidal anhydrous silica, microcrystalline cellulose and magnesium stearate and either the coating Opadry Yellow 45F32810 (100 mg tablet) or Opadry Grey OY-GM-27600 (400 mg tablet).

Opadry Yellow 45F32810 (100 mg tablet) and Opadry Grey OY-GM-27600 (400 mg tablet) are made up of the excipients polydextrose, hypromellose, titanium dioxide (E171), macrogol, iron oxide yellow (E172) and iron oxide black (E172 –400mg
Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry Yellow 45F32810 and Opadry Grey OY-GM-27600, which are controlled to suitable in-house specifications. However their components are controlled to their respective European Pharmacopoeia monographs, with the exception of polydextrose and iron oxide black (E172), which are controlled to suitable in-house specifications, and iron oxide yellow (E172) which is compliant with its National Formulary specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Myambutol Tablets 100 mg and 400 mg (Genus Pharmaceuticals, UK). Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of both strengths of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

**Control of Finished Product**

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

**Container Closure System**

The tablets are packaged in either:

1. aluminium/polyvinylchloride/aluminium blisters packed with the Patient Information Leaflet into cardboard outer cartons, in a pack size of 56 tablets
2. polypropylene tablet containers, in pack size of 56 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for
marketing. Based on the results, a shelf-life of 3 years has been proposed, with the storage conditions ‘Do not store above 25°C.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PIL and labelling are satisfactory from a pharmaceutical perspective. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant competent authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) Forms
The MAA forms are acceptable from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of ethambutol hydrochloride are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of ethambutol hydrochloride is well-known. With the exception of data from the bioequivalence study described below, no new pharmacodynamic or pharmacokinetic data were provided or required for these applications.

Pharmacokinetics
In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

An open label, single dose, balanced, randomised, two-treatment, two-period, crossover study comparing the pharmacokinetics of the test product Ethambutol tablets 400 mg (manufactured by Cipla Ltd, India) and the reference product Myambutol tablets 400 mg (Riemser Arzneimittel, Germany) in healthy adult male subjects under fasting conditions.

The subjects were administered one tablet (400 mg) of either the test or the reference product with 240 ml of water, after an overnight fast. Blood samples were collected before and up to 72 hours after each administration. The washout period between the treatment phases was 13 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ethambutol 400 mg (Test)</th>
<th>Myambutol 400 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>1028.52</td>
<td>999.15</td>
<td>103.01</td>
<td>92.02-115.32</td>
</tr>
<tr>
<td>AUC_{0-t} (hr.ng/ml)</td>
<td>6397.85</td>
<td>6300.45</td>
<td>101.56</td>
<td>96.34-107.06</td>
</tr>
<tr>
<td>AUC_{0-inf} (hr.ng/ml)</td>
<td>6980.10</td>
<td>6873.88</td>
<td>101.56</td>
<td>96.64-106.73</td>
</tr>
</tbody>
</table>

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from log-transformed data

The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00 to 125.00 % for AUC and C_{max} values. Thus, the data support the claim that the applicant’s test product Ethambutol tablets 400 mg is bioequivalent to the reference product Myambutol tablets 400 mg (Riemser Arzneimittel, Germany) under fasting conditions.

As the 100 mg and 400 mg strength products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 400 mg tablet strength can be extrapolated to the 100 mg strength tablet.

EFFICACY
The efficacy of ethambutol hydrochloride is well-known. No new efficacy data have been submitted and none are required for applications of this type.
SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised by the bioequivalence data.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and 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 either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in line with the current guidelines. The labelling is in line with the current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Ethambutol 100 mg and 400 mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of ethambutol hydrochloride are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none were required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Ethambutol 400 mg Tablets and the reference product Myambutol tablets 400 mg (Riemser, Arzneimittel, Germany). A biowaiver has been granted to the 100 mg strength tablet based on the study conducted, in line with the current bioequivalence guideline.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none were required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference product, where appropriate, along with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ethambutol hydrochloride is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 13 May 2010.
2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 08 June 2010.
3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 30 July 2010 and 21 March 2011, and to the quality dossier on 16 September 2010, 16 November 2011, 12 April 2012, 15 August 2012 and 11 October 2012.
4 The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 02 March 2011 and 14 February 2012, and on the quality dossier on 30 March 2012, 30 July 2012, 10 October 2012 and 18 October 2012.
5 The applications were granted on 16 November 2012.
SUMMARY OF PRODUCT CHARACTERISTICS
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET
In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.