UK Public Assessment Report

Isoniazid 100 mg Tablets

PL 20117/0233

Morningside Healthcare Limited
Lay Summary
Isoniazid 100 mg Tablets
(isoniazid)

This is a summary of the Public Assessment Report (PAR) for Isoniazid 100 mg Tablets (PL 20117/0233). It explains how Isoniazid 100 mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Isoniazid 100 mg Tablets.

For practical information about using Isoniazid 100 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Isoniazid 100 mg Tablets and what are they used for?
Isoniazid 100 mg Tablets contain the active substance isoniazid. Isoniazid 100 mg Tablets are used to treat and prevent tuberculosis (TB), an infectious disease mainly affecting the lungs.

Isoniazid 100 mg Tablets are a ‘generic’ medicine. This means that Isoniazid 100 mg Tablets are similar to a reference medicine already authorised in the European Union (EU) called Isozid 100 mg Tablets (Riemser Arzneimittel AG., Germany).

How do Isoniazid 100 mg Tablets work?
Isoniazid is an antibiotic, which kills the bacterium that causes tuberculosis.

How are Isoniazid 100 mg Tablets used?
Isoniazid 100 mg Tablets can be obtained only with a prescription. The medicine should be taken exactly as advised by the doctor.

Isoniazid 100 mg Tablets are taken by mouth.

For adults, the recommended dose is dependent on bodyweight. The maximum dose is three (3) of the 100 mg tablets daily. For the treatment of tuberculosis meningitis, a higher dose may be given, particularly during the first 1 to 2 weeks of treatment.

For elderly patients, lower doses may be needed if the liver and kidneys are not working well.

Use in children
The dose in children is dependent on body weight, and can be given in single or divided doses.

For further information on how Isoniazid 100 mg Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the MHRA website.

What benefits of Isoniazid 100 mg Tablets have been show in studies?
As Isoniazid 100 mg Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Isozid 100 mg Tablets (Riemser Arzneimittel AG., Germany). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
In addition, the company (Morningside Healthcare Limited) have provided data from the published literature on isoniazid.

**What are the possible side effects of Isoniazid 100 mg Tablets?**
Because Isoniazid 100 mg Tablets are a generic medicine and are bioequivalent to the reference medicine, the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of restrictions, see the package leaflet available on the Medicines and Healthcare products Regulatory Agency website.

**Why are Isoniazid 100 mg Tablets approved?**
It was concluded that, in accordance with EU requirements, Isoniazid 100 mg Tablets have been shown to have comparable quality and to be bioequivalent to Isozid 100 mg Tablets (Riemser Arzneimittel AG., Germany). Therefore, the view was that, as for Isozid 100 mg Tablets (Riemser Arzneimittel AG., Germany), the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Isoniazid 100 mg Tablets?**
Known side-effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Isoniazid 100 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Isoniazid 100 mg Tablets.**
A Marketing Authorisation was granted in the UK on 17 July 2014.

The full PAR for Isoniazid 100 mg Tablets follows this summary.

For more information about treatment with Isoniazid 100 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2015.
# Table of Contents

I  Introduction  
   Page 5  
II  Quality aspects  
   Page 6  
III  Non-clinical aspects  
    Page 8  
IV  Clinical aspects  
    Page 8  
V   User consultation  
    Page 10  
VI  Overall conclusion, benefit/risk assessment and recommendation  
    Page 10  

Table of content of the PAR update  
Page 13
I  Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited a Marketing Authorisation for the medicinal product Isoniazid 100 mg Tablets (PL 20117/0233). The product is a prescription-only medicine (POM) indicated for the treatment of all forms of pulmonary and extra-pulmonary tuberculosis.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to Isozid 100mg Tablets, licensed on 21 September 2005 in Germany to Riemser Arzneimittel AG. Isozid 100 mg Tablets was first granted prior to 1978 and then was subsequently licenced under the current Marketing Authorisation in 2005. The equivalent medicinal product marketed in the UK is Isoniazid 100 mg tablets (PL 00039/5780R) authorised on 16/01/1991 to UCB Pharma Ltd and cancelled on the 1st February 2002.

The active ingredient, isoniazid, is bactericidal against *Mycobacterium tuberculosis*, possibly acting via interference with the synthesis of mycolic acid (a constituent of the bacterial cell wall).

One bioequivalence study was submitted to support this application comparing the applicant’s test product Isoniazid 300 mg Tablets (x1) with the reference Isozid 100 mg (x 3; Fatol Arzneimittel GMBH, Schiffweiler, Germany) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being a generic medicinal product of an originator product that has 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 Isoniazid 100 mg tablets outweigh the risks and a Marketing Authorisation was granted.

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.
II Quality aspects

II.1 Introduction
This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to Isozid 100mg Tablets, licensed on 21 September 2005 in Germany to Riemser Arzneimittel AG. Isozid 100mg Tablets was first granted prior to 1978 and then was subsequently licenced under the current Marketing Authorisation in 2005. The equivalent medicinal product marketed in the UK is Isoniazid 100mg tablets (PL 00039/5780R) authorised on 16/01/1991 to UCB Pharma Ltd and cancelled on the 1st February 2002.

Isoniazid 100 mg Tablets are formulated as white, circular, biconvex, uncoated tablets having plain surfaces on both sides.

Each tablet contains 100 mg of the active ingredient isoniazid. The excipients present in each tablet are: calcium hydrogen phosphate, maize starch (dried), purified talc, colloidal anhydrous silica and magnesium stearate.

Sumatriptan 50 mg and 100 mg Tablets are packed in white opaque polyvinylchloride/aluminium/polyvinylidene chloride/aluminium (PVC/PVdC/Alu) blisters. The blisters are packed with the Patient Information Leaflet in outer cartons in pack sizes of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100 and 112 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.

II.2 Drug Substance
Isoniazid
INN: Isoniazid

![Isoniazid molecule]

Molecular formula: C_{6}H_{7}ON_{3}O
Molecular weight: 137.1
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Freely soluble in water, sparingly soluble in alcohol.

Isoniazid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, isoniazid, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3  Medicinal Product

Pharmaceutical development
The objective of the development programme was to formulate a safe efficacious, stable dosage form bioequivalent to the reference product Isozid 100 mg Tablets (Riemser Arzneimittel AG, Germany).

Suitable pharmaceutical development data have been provided for this application.

Comparable in-vitro dissolution profiles have been provided for this product and the reference product.

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

Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective Pharmacopoeia monographs.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

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.

Manufacture of the product
A satisfactory description of the manufacturing process and batch formulae for the drug product has been provided. The manufacturing process has been validated with full-scale production-scale batches and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with the special storage conditions ‘Store below 25°C.

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

II.4  Discussion on chemical, pharmaceutical and biological aspects
The MAA form is satisfactory from a pharmaceutical perspective.
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The grant of a Marketing Authorisation is recommended.

III  Non-clinical aspects
As the pharmacodynamic, pharmacokinetic and toxicological properties of isoniazid are well known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Environmental Risk Assessment (ERA)
As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.

IV  Clinical aspects

IV.1  Introduction
As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

IV.2  Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

A single centre, open label, randomised, single dose, two-way crossover study to compare the pharmacokinetics of the applicant’s test product Isoniazid 300mg versus the reference product Isozid 100 mg (x 3; Fatol Arzneimittel GmbH, Schiffweiler, Germany) in healthy adult male and female subjects under fasting conditions.

The subjects were administered a single dose (300 mg) of either the test (one 300 mg tablet) or the reference product (three 100 mg tablets) with 240 ml of water, after at least a 10-hour overnight fast. Water was permitted ad lib until 1 hour before dosing and again 2 hours after dosing. Standardised meals were provided at 4 hours post drug administration and at other relevant times.

Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:
The 90% confidence intervals of the test/reference ratio for AUC, and Cmax values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product (x3) Isoniazid 100 mg (Fatol Arzneimittel GmbH, Schiffweiler, Germany).

As the 100 mg and 300 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 300 mg tablet strength can be extrapolated to the 100 mg strength tablet.

IV.3 Pharmacodynamics
No new pharmacodynamics data have been submitted and none are required for this type of application.

IV.4 Clinical efficacy
The efficacy of isoniazid is well-known. No new efficacy data have been submitted and none are required for this type of application.

IV.5 Clinical safety
With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised during the bioequivalence study.

IV.6 Risk Management Plan (RMP)
No Risk Management Plan has been submitted and none was required. This application was received prior to 21 July 2012, the date from which...
pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the application is for substitution of an already authorised product, for which safety concerns requiring additional risk minimisation have not been identified, there is no need for a detailed European Risk Management Plan and the routine pharmacovigilance activities are sufficient. The reference product has been in use for many years and the safety profile of the active ingredient is well-established.

IV.7 Discussion on the clinical aspects
The SmPC, PIL and labelling are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with current guidance. The labelling is also in line with current guidance.

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The grant of a Marketing Authorisation is recommended.

V User consultation
A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to a package leaflet for Pyrazinamide 500mg Tablets, PL 20117/0014. The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation

Quality
The quality characteristics of Isoniazid 100 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 isoniazid are well-known, no additional data were required.

Efficacy
With the exception of the bioequivalence study, no new clinical data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s product Isoniazid 300 mg and the reference product Isozid 100 mg x 3 (Fatol Arzneimittel GmbH, Schiffweiler, Germany), under fasting conditions.
As the 100 mg and 300 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 300 mg tablet strength can be extrapolated to the 100 mg strength tablet.

**Safety**

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of isoniazid is well-known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

**Benefit/risk assessment**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with isoniazid is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for these products are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labelling text is listed below:
Each tablet contains 100mg of the active ingredient, isoniazid.

**DOSAGE:** To be taken as directed by your doctor.
For oral use.
This medicine contains starch. See package leaflet for further information.

**KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.**
Read the package leaflet before use.
Do not store above 25°C.
# Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval / non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update the package leaflet to remove the warning &quot;Isonazid tablets contain starch&quot; as per the EMA excipients guideline for labelling.</td>
<td>Yes</td>
<td>06 March 2015</td>
<td>20 March 2015</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 20117/0233 – 0003
Product: Isoniazid 100 mg Tablets
Marketing Authorisation Holder: Morningside Healthcare Limited
Active Ingredient: Isoniazid

Reason:
To update the package leaflet to remove the warning "Isoniazid tablets contain starch", as per the European Medicines Agency excipients guideline for labelling.

Supporting Evidence
An updated version of the package leaflet is presented.

Evaluation
The updated package leaflet reflects the proposed change and minor typographical corrections. This is acceptable.

The current approved UK versions of the SmPC and PIL for this product are available on the Medicines and Healthcare products Regulatory Agency website.

Decision: Granted
Date: 20 March 2015