Pyrazinamide 500 mg tablets

PL 20117/0014

UKPAR

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LAY SUMMARY

Pyrazinamide 500 mg tablets
(pyrazinamide, tablets, 500 mg)

This is a summary of the Public Assessment Report (PAR) for Pyrazinamide 500 mg tablets (PL 20117/0014). It explains how Pyrazinamide 500 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 Pyrazinamide 500 mg tablets.

For practical information about using Pyrazinamide 500 mg tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Pyrazinamide 500 mg tablets and what are they used for?
Pyrazinamide 500 mg tablets are a medicine that contains the active substance pyrazinamide. Pyrazinamide tablets are used for treating tuberculosis, commonly called “TB”. Pyrazinamide tablets are always given in combination with other antituberculosis agents.

Pyrazinamide 500 mg tablets are a ‘generic’ medicine. This means that Pyrazinamide 500 mg tablets are similar to a reference medicine already authorised in the European Union (EU) called PYRAFAT 500 mg film-coated tablets (RIEMSER Arzneimittel AG, Germany).

How are Pyrazinamide 500 mg tablets used?
Pyrazinamide 500 mg tablets are taken by mouth.

The recommended doses are as detailed below:

- **Adults and the elderly**
The usual dose is 3 tablets or 1.5 g daily for patients weighing under 50 kg and whose medication is not supervised by a doctor on a daily basis. For patients weighing more than 50 kg, the dose may be increased to 4 tablets or 2 g daily.

In cases where the patient’s medication is supervised by a doctor on a daily basis, the dose for adults under 50 kg is a maximum of 4 tablets or 2 g, three times a week. For patients who weigh over 50 kg, the dose is a maximum of 5 tablets or 2.5 g, three times a week.

The number of tablets that should be taken each day will depend on the patient’s kidney function and bodyweight.

- **Children**
Pyrazinamide 500 mg tablets are supplied according to the weight of the child. If the medication is not supervised on a daily basis, the dose is 35 mg/kg daily. If the medication is supervised on a daily basis, the dose is 50 mg/kg, three times a week.

The prescribing doctor will decide on the duration of treatment.

In standard tuberculosis treatment, Pyrazinamide 500 mg tablets are given together with other anti-tuberculosis medication during the initial phase of treatment for a total of 8 weeks.

For further information on how Pyrazinamide 500 mg tablets are used, refer to the Summary of Product Characteristics.
Pyrazinamide 500 mg tablets can only be obtained on prescription.

**How do Pyrazinamide 500 mg tablets work?**
The active substance, pyrazinamide, works by killing a particular type of germ which causes tuberculosis.

**How have Pyrazinamide 500 mg tablets been studied?**
Because Pyrazinamide 500 mg tablets are a generic medicine, studies in patients have been limited to bioequivalence tests to determine that they are similar to the reference medicine, PYRAFAT 500 mg film-coated 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) has provided data from the published literature on pyrazinamide.

**What are the benefits and risks of Pyrazinamide 500 mg tablets?**
Because Pyrazinamide 500 mg tablets are a generic medicine and are bioequivalent to the reference medicine, their benefits and risks are taken as being the same as the reference medicine.

**Why are Pyrazinamide 500 mg tablets approved?**
It was concluded that, in accordance with EU requirements, Pyrazinamide 500 mg tablets have been shown to have comparable quality and to be bioequivalent to PYRAFAT 500mg film-coated tablets (RIEMSER Arzneimittel AG, Germany). Therefore, the view was that, as for PYRAFAT 500mg film-coated tablets (RIEMSER Arzneimittel AG, Germany), the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Pyrazinamide 500 mg tablets?**
A Risk Management Plan has been developed to ensure that Pyrazinamide 500 mg tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Pyrazinamide 500 mg tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Pyrazinamide 500 mg tablets.**
A Marketing Authorisation was granted in the UK on 20 December 2013.

The full PAR for Pyrazinamide 500 mg tablets follows this summary.

For more information about treatment with Pyrazinamide 500 mg tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2014.
Pyrazinamide 500 mg tablets

PL 20117/0014

SCIENTIFIC DISCUSSION

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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 Pyrazinamide 500 mg tablets (PL 20117/0014) on 20 December 2013. This product is a prescription-only medicine (POM) indicated in patients with active tuberculosis caused by *Mycobacterium tuberculosis*. Pyrazinamide should only be given in combination with other antituberculous agents. Pyrazinamide is not active against atypical mycobacteria.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross-referring to PYRAFAT 500 mg film-coated tablets (RIEMSER Arzneimittel AG, Germany), which was first authorised in Germany on 29 January 1987. The comparator product in the UK is Zinamide 500 mg tablets (PL 06831/0206), which was licensed to Genus Pharmaceuticals Limited on 12 October 2007 following a Change of Ownership (COA) procedure with PL 00025/5038R (Merck Sharp & Dohme Limited). Zinamide 500 mg tablets (PL 00025/5038R, Merck Sharp & Dohme Limited) was granted on 21 July 1986 following the product licence review of Zinamide tablets PLR 00025/5038, which was granted a Product Licence of Right in February 1973.

The active ingredient, pyrazinamide, is a prodrug that is converted into its active form, pyrazinoic acid, by a mycobacterial enzyme, pyrazinamidase, as well as through hepatic metabolism. Pyrazinoic acid is bactericidal to *Mycobacterium tuberculosis* at acid pH values but not at neutral pH. The precise mechanism of action is unknown. Pyrazinamide is inactive against atypical mycobacteria. Resistance develops rapidly if pyrazinamide is used as sole anti-tuberculosis agent, pyrazinamide should only be used in combination with other anti-tuberculosis agents.

One bioequivalence study was submitted to support this application comparing the applicant’s test product Pyrazinamide 500 mg tablets with the reference product PYRAFAT 500 mg film-coated tablets (pyrazinamide; RIEMSER Arzneimittel AG, Germany) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with EMEA guidelines, Directive 2001/20/EC and ICH GCP Guidelines including archiving of essential documents and current version of Declaration of Helsinki.

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 Pyrazinamide 500 mg tablets outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Pyrazinamide
Chemical name: Pyrazine-2-carboxamide
IUPAC: Pyrazine-2-carboxamide; Pyrazinocarboxamide

Structure:

\[
\text{C}_5\text{H}_5\text{N}_3\text{O}
\]

Molecular formula: \( \text{C}_5\text{H}_5\text{N}_3\text{O} \)
Molecular weight: 123.11
Appearance: White crystalline powder
Solubility: Sparingly soluble in water, slightly soluble in alcohol and methylene chloride and very slightly soluble in ether.

Pyrazinamide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance pyrazinamide, except for stability data to support a suitable retest period when stored in the proposed packaging, are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

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 lactose monohydrate, maize starch, pregelatinised starch, talc, colloidal anhydrous silica and hydrogenated castor oil. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs.

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

With the exception of lactose monohydrate, none of the excipients contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate.

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 tablets that were comparable in performance to the innovator product PYRAFAT 500 mg film-coated 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, the reference product, PYRAFAT 500mg film-coated tablets (Riemser Arzneimittel AG, Germany) and the comparator product in the UK, Zinamide 500 mg tablets (Genus Pharmaceuticals Limited, UK).

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale production-scale batches 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 specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packed in:
1. Polyvinylchloride-polyvinylidene chloride/aluminum (PVC-PVDC/Alu) blisters containing 10, 14, 28, 30, 50, 56, 60, 90, 100, 120 and 500 tablets.
2. High-density polyethylene (HDPE) containers with polypropylene (PP) caps containing 10, 14, 28, 30, 50, 56, 60, 90, 100, 120 and 500 tablets.

Not all pack sizes may be marketed.

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. The data from these studies support a shelf-life of 24 months for the blister pack and 48 months for the closed HPDE container. After opening the HDPE container pack, the tablets should be used within 6 months (180 days). This medicinal product does not require any special storage conditions.

After opening the HDPE container pack, the tablets should be used within 6 months (180 days).

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

Bioequivalence
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

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) Form
The MAA form is satisfactory 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 a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

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

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
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
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.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of pyrazinamide is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence study:

A randomised, open label, two-treatment, two-sequence, two-period, single-dose, crossover study to compare the pharmacokinetics of the test product Pyrazinamide 500 mg Tablets versus the reference product PYRAFAT 500 mg Tablets (pyrazinamide; RIEMSER Arzneimittel AG, Germany) in healthy adult male subjects under fasting conditions.

The subjects were administered a single dose (one tablet) of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was at least 8 days. The parent compound pyrazinamide was analysed. Bioequivalence was to be declared if the 90% confidence intervals of the test/reference ratio of geometric means for C\text{max} and AUC\text{0-t} values were 80.00% to 125.00% for pyrazinamide. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) for pyrazinamide

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<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90 % Confidence Interval for Log-transformed data</th>
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<td>Reference (B)</td>
<td>A/B</td>
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<td>AUC\text{0-t}</td>
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<td>C\text{max}</td>
<td>12879.98</td>
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<td>106.5694</td>
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</table>

Test product-A Pyrazinamide 500mg Tablets (Morningside Healthcare Limited)
Reference product-B PYRAFAT® Tablets 500 mg (pyrazinamide; RIEMSER Arzneimittel AG, Germany)
C\text{max} maximum plasma concentration
AUC\text{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\text{0-inf} area under the plasma concentration-time curve from time zero to infinity hours
* Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data

Discussion and conclusion

Pyrazinamide is considered to have a narrow therapeutic index, hepatotoxicity being the main problem associated with the drug. The Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits for narrow therapeutic index drugs as 90.00% to 111.11% for AUC values as well as for C\text{max} values where C\text{max} is of particular importance for safety, efficacy or drug level monitoring. The protocol specified 80.00% to 125.00% as criteria for bioequivalence. Although the pre-specified criteria were not narrowed in line with the applicable guidance, the actual results indicate that AUC\text{0-t} falls within the narrow margin criteria, while C\text{max} is just outside those margin. The applicant has provided adequate justification to support the claim that C\text{max} is not of particular relevance for the safety or efficacy of pyrazinamide.
Thus, the data support the claim that the applicant’s test product Pyrazinamide 500 mg Tablets is bioequivalent to the reference product PYRAFAT 500 mg Tablets (RIEMSER Arzneimittel AG, Germany) under fasting conditions.

**EFFICACY**
The efficacy of pyrazinamide is well-known. No new efficacy data have been submitted and none are required for this type of application.

**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.

**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.

An acceptable Risk Management Plan for the product has been submitted. Routine risk minimisation measures as per the proposed Summary of Product Characteristics (SmPC) are proposed. There are no additional risk minimisation measures.

**SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**
The SmPC, PIL and labelling are acceptable from a clinical perspective. The SmPC is consistent with that for the reference products. 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.

**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 a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Pyrazinamide 500 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 pyrazinamide are well-known, no additional data were required.

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

Bioequivalence has been demonstrated between the applicant’s Pyrazinamide 500 mg tablets and the reference product PYRAFAT 500 mg Tablets (RIEMSER Arzneimittel AG, Germany under fasting conditions.

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 pyrazinamide is well-known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

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 pyrazinamide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Pyrazinamide 500 mg tablets

PL 20117/0014

STEP TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 26 February 2013.
2 Following standard checks and communication with the applicant the MHRA considered the application valid on 01 March 2013.
3 Following assessment of the application the MHRA requested further information relating to the dossier on 31 May 2013, 08 October 2013 and 20 November 2013.
4 The applicant responded to the MHRA’s requests, providing further information on the dossier on 16 August 2013, 07 November 2013, 21 November 2013 and 22 November 2013.
5 The application was granted on 20 December 2013.
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.