Public Assessment Report

Decentralised Procedure

Rizatriptan 5 mg and 10 mg Tablets
Rizatriptan 5 mg and 10 mg Orodispersible Tablets

Rizatriptan benzoate

UK/H/3396/001-2/DC
UK/H/3397/001-2/DC

UK licence no: PL 18909/0383-6

Arrow Generics Limited
LAY SUMMARY

On 12th December 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) to Arrow Generics Limited for the medicinal products Rizatriptan 5 mg and 10 mg Tablets/Orodispersible Tablets (PL 18909/0383-6, UK/H/3396-7/001-2/DC). These are prescription-only medicines (POM).

Rizatriptan Tablets belongs to a class of medicines called selective serotonin 5-HT1B/1D receptor agonists.

Rizatriptan Tablets are used to treat the headache phase of the migraine attack in adults.

Treatment with Rizatriptan:

Rizatriptan reduces swelling of the blood vessels surrounding the brain. This swelling results in the headache pain of a migraine attack.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Rizatriptan 5 mg and 10 mg Tablets/Orodispersible Tablets outweigh the risks. Hence Marketing Authorisations have been granted.
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# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Rizatriptan 5 mg and 10 mg Tablets/Orodispansible Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Rizatriptan (as rizatriptan benzoate)</td>
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<tr>
<td><strong>Form</strong></td>
<td>Tablets/Orodispansible Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5 mg and 10 mg</td>
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</table>
| **MA Holder** | Arrow Generics Ltd  
Unit 2, Eastman Way,  
Stevenage, Herts,  
SG1 4SZ, UK |
| **RMS** | UK |
| **CMS** | UK/H/3396/01/DC: Denmark, Germany, Italy, Malta, Sweden and The Netherlands  
UK/H/3396/02/DC: Denmark, Finland, Germany, Italy, Malta, Spain, Sweden and The Netherlands  
UK/H/3397/01/DC: Denmark, Germany, Greece, Malta, Sweden and The Netherlands  
UK/H/3397/02/DC: Denmark, Finland, Germany, Greece, Malta, Spain, Sweden, Italy and The Netherlands |
| **Procedure Numbers** | UK/H/3396-7/01-02/DC |
| **Timetable** | Day 210 – 10\(^{th}\) October 2012 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the applications for Rizatriptan 5 mg and 10 mg Tablets/Orodispersible Tablets in the treatment of acute treatment of the headache phase of migraine attacks, with or without aura in adults could be approved.

These applications were submitted under Article 10.1 of Directive 2001/83/EC (as amended). The applicant cross-refer to MAXALT 5 mg and 10 mg Tablets (PL 00025/0369 and 0370), first authorised to Merk Sharp & Dohme Ltd on 24th June 1998.

With the UK as the RMS in these Decentralised Procedures, Arrow Generics Limited applied for Marketing Authorisations for Rizatriptan 5 mg and 10 mg Tablets (UK/H/3396/001-2/DC) and for Rizatriptan 5 mg and 10 mg Orodispersible Tablets (UK/H/3397/001-2/DC) in the following CMSs:

UK/H/3396/01/DC: Denmark, Germany, Italy, Malta, Sweden and The Netherlands
UK/H/3396/02/DC: Denmark, Finland, Germany, Italy, Malta, Spain, Sweden and The Netherlands
UK/H/3397/01/DC: Denmark, Germany, Greece, Malta, Sweden and The Netherlands
UK/H/3397/02/DC: Denmark, Finland, Germany, Greece, Malta, Spain, Sweden, Italy and The Netherlands

Rizatriptan binds selectively with high affinity to human 5-HT1B and 5-HT1D receptors and has little or no effect or pharmacological activity at 5-HT2 or 5-HT3, adrenergic alpha1, alpha2 or beta; D1, D2, dopaminergic, histaminic H1; muscarinic; or benzodiazepine receptors.

The therapeutic activity of rizatriptan in treating migraine headache may be attributed to its agonist effects at 5-HT1B and 5-HT1D receptors on the extracerebral intracranial blood vessels that are thought to become dilated during an attack and on the trigeminal sensory nerves that innervate them. Activation of these 5-HT1B and 5-HT1D receptors may result in constriction of pain-producing intracranial blood vessels and inhibition of neuropeptide release that leads to decreased inflammation in sensitive tissues and reduced central trigeminal pain signal transmission.

No new non-clinical and clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. Bioequivalence studies were 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 these product types at all sites responsible for the manufacture and assembly of these products.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that 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 the non-submission of a Risk Management Plan (RMP).

All involved Member States agreed to grant Marketing Authorisations for the above products at the end of the procedures (Day 210 – 10th October 2012). After a subsequent national phase, the UK granted Marketing Authorisations for these products on 12th December 2012 (PL 18909/0383-6).
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Rizatriptan 5 mg and 10 mg Tablets/Orodispensible Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Rizatriptan benzoate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>N02CC04, Selective serotonin (5HT1B/1D) agonist</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Tablets/Orodispensible Tablets, 5 mg and 10 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedures</td>
<td>UK/H/3396-7/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td></td>
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<tr>
<td></td>
<td><strong>UK/H/3396/01/DC</strong>: Denmark, Germany, Italy, Malta, Sweden and The Netherlands</td>
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<td></td>
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<tr>
<td></td>
<td><strong>UK/H/3397/02/DC</strong>: Denmark, Finland, Germany, Greece, Malta, Spain, Sweden, Italy and The Netherlands</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 18909/0383-6</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Arrow Generics Ltd</td>
</tr>
<tr>
<td></td>
<td>Unit 2, Eastman Way,</td>
</tr>
<tr>
<td></td>
<td>Stevenage, Herts,</td>
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<tr>
<td></td>
<td>SG1 4SZ, UK</td>
</tr>
</tbody>
</table>
III    SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

rINN: Rizatriptan benzoate

Chemical Name:
\[ N,N\text{-Dimethyl}-2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethanamine \]

Benzoate

Structure:

\[
\begin{align*}
\text{Molecular Formula: } & C_{22}H_{25}N_5O_2 \\
\text{Molecular Weight: } & 391.5 \\
\text{Appearance: } & \text{A white to off-white powder, soluble in water, sparingly soluble in ethanol (96 per cent) and slightly soluble in methylene chloride.} \\
\text{The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.} \\
\text{Synthesis of the drug substance from the designated starting material(s) has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.} \\
\text{An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.} \\
\text{Batch analysis data are provided, which comply with the proposed specification.} \\
\text{Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.} \\
\text{Appropriate stability data have been generated to support a suitable retest period when the drug substance is stored in the proposed packaging.} \\
\end{align*}
\]

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol, sorbitol (E420), Iron oxide red, crospovidone, colloidal anhydrous silica and magnesium stearate (Rizatriptan 5
mg and 10 mg Tablets) and mannitol, sorbitol (E420), crospovidone, saccharin sodium, natural peppermint flavour, silica, colloidal anhydrous and magnesium stearate (Rizatriptan 5 mg and 10 mg Orodispersible Tablets).

All excipients comply with their respective European Pharmacopoeia monographs except Iron oxide red which complies with the United States Pharmacopoeia and natural peppermint flavour complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient in the products that contain material of animal or human origin is magnesium stearate. Confirmation has been given that the magnesium stearate is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablet/Orodispersible Tablet that contains the same active ingredient as MAXALT 5 mg and 10 mg Tablets (Merk Sharp & Dohme Ltd).

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and dissolution profiles have been presented for the proposed and reference products.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished Product Specification**

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

**Container-Closure System**

The finished product is packed in Aluminium foil/foil blister packs with 2, 3, 6, 12 or 18 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with relevant EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.
Based on the results, a shelf-life of 3 years with no special storage condition is set. This is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPCs, PILs and labels are acceptable from a pharmaceutical perspective.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant, making reference to the user-testing of the PIL for Zolmitriptan 2.5 mg and 5 mg film-coated tablets and Sumatriptan 50 mg and 100 mg Tablets. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use of the products were similar for both leaflets. The justification of the rationale for bridging is accepted.

The Marketing Authorisation Holder has committed to submit mock-ups for un-marketed pack sizes to the relevant regulatory authorities for approval before those packs are marketed.

**Marketing Authorisation Application (MAA) Forms**

The MAA forms are satisfactory from a pharmaceutical perspective.

**Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

There are no objections to the approval of these products from a pharmaceutical point of view.

**III.2 NON-CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of rizatriptan benzoate are well known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Suitable justification has been provided for the non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical point of view.

**III.3 CLINICAL ASPECTS**

In support of these applications, the Marketing Authorisation holder has submitted the following bioequivalence studies.

**Rizatriptan 5 mg and 10 mg Tablets (PL 18909/0383-4)**

This is an open label, randomised, two period, two sequence, single dose, crossover bioequivalence study comparing Rizatriptan 10 mg Tablets with the reference product Maxalt® 10 mg Tablets in 44 healthy adult volunteers under fasting conditions.
Blood samples were collected prior to and 0.08, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 10 and 12 hours after drug administration. The wash out period was 7 days.

The main pharmacokinetic parameters (geometric mean) of Rizatriptan (N = 44)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INTRA-SUBJECT C.V. (%)</th>
<th>GEOMETRIC LSMEANS *</th>
<th>RATIO (%)</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>19.5</td>
<td>21.536</td>
<td>22.291</td>
<td>96.61</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;</td>
<td>8.5</td>
<td>68.936</td>
<td>72.222</td>
<td>95.45</td>
</tr>
</tbody>
</table>

* units are ng/mL for C<sub>max</sub> and ng.h/mL for AUC<sub>T</sub>

Rizatriptan 5 mg and 10 mg Orodispersible Tablets (PL 18909/0385-6)

This is an open label, randomised, two period, two sequence, single dose, crossover bioequivalence study comparing Rizatriptan 10 mg Orodispersible Tablets with the reference product Maxalt<sup>®</sup> Melt 10 mg Tablets in 33 healthy adult volunteers under fasting conditions.

Blood samples were collected prior to and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 10 and 12 hours after drug administration. The wash out period was 7 days.

Results

The main pharmacokinetic parameters (geometric mean) of Rizatriptan (N = 32/33)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INTRA-SUBJECT C.V. (%)</th>
<th>GEOMETRIC LSMEANS *</th>
<th>RATIO (%)</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>18.3</td>
<td>18.178</td>
<td>19.691</td>
<td>92.32</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;</td>
<td>12.2</td>
<td>67.116</td>
<td>71.307</td>
<td>94.12</td>
</tr>
</tbody>
</table>

* units are ng/mL for C<sub>max</sub> and ng.h/mL for AUC<sub>T</sub>

The 90% confidence intervals for C<sub>max</sub> and AUC<sub>T</sub> were within the pre-defined limits. Bioequivalence has been shown for the test formulations (Rizatriptan 10 mg Tablets and
Rizatriptan 10 mg Orodispersible Tablets) and the reference formulations (Maxalt® 10 mg Tablets and Maxalt® Melt 10 mg Tablets). According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the studies for 10 mg formulations can be extrapolated to the other strengths i.e. 5 mg Tablets or 5 mg Orodispersible Tablets.

**Pharmacodynamics**
No new data have been submitted and none are required.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.

**Expert Report (Clinical Overall Summary)**
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

**Module 1 – Administrative information**
*Marketing Authorisation Application forms (MAA)*
The MAA forms are satisfactory from a clinical perspective.

*Summary of Product Characteristics (SmPC)*
The SmPCs are satisfactory from a clinical perspective and consistent with those for the reference products.

*Patient Information Leaflet (PIL)*
The PIL is satisfactory from a clinical perspective and consistent with the SmPCs.

**Packaging**
The packaging is satisfactory from a clinical perspective.

**Conclusion**
There are no objections to the approval of these products from a clinical point of view.

**IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Rizatriptan 5 mg and 10 mg Tablets/Orodispersible 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 Rizatriptan 10 mg Tablets and Rizatriptan 10 mg Orodispersible Tablets and the reference products, Maxalt® 10 mg
tablets and Maxalt® Melt 10 mg Tablets. The results of the bioequivalence study for the 10 mg formulations can be extrapolated to 5 mg strengths.

SAFETY
No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE
The SmPCs and PILs are satisfactory and consistent with those for the reference products. Satisfactory labelling has been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with rizatriptan benzoate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit balance is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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