COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rizatriptan Passauer 5 mg and 10 mg orodispersible tablets

(rizatriptan benzoate)

NL/H/4263/001-002/DC

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Rizatriptan Passauer 5 mg and 10 mg orodispersible tablets. The procedure was finalised at 1 November 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rizatriptan Passauer 5 mg and 10 mg orodispersible tablets from Passauer Pharma GmbH.

The product is indicated for acute treatment of the headache phase of migraine attacks with or without aura in adults. A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Maxalt Smelt 5 mg and 10 mg orodispersible tablets (NL licence RVG 21817 and 21818) which has been registered in the Netherlands by Merck Sharp & Dohme since 11 February 1998 (original product).

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Rizatriptan Passauer is an orodispersible tablet:

- Rizatriptan Passauer 5 mg orodispersible tablets are white to off-white coloured, round flat bevelled tablets with a diameter of 9.0 mm.
- Rizatriptan Passauer 10 mg orodispersible tablets are white to off-white coloured, round, flat bevelled tablets with a diameter of 10.5 mm.

Each tablet contains 7.265 mg or 14.530 mg of rizatriptan benzoate equivalent to 5 mg or 10 mg of rizatriptan.

The orodispersible tablets are packed in peel-off aluminium/aluminium blister packs.

The excipients are

- lactose monohydrate
- microcrystalline cellulose (E460a)
- calcium silicate (E552)
- crospovidone (E1202)
- aspartame (E951)

- peppermint flavour:
  components: maize maltodextrin and modified waxy maize starch (E1450)
- colloidal anhydrous silica (E511)
- magnesium stearate (E470b)

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is rizatriptan benzoate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is soluble in water. The active substance displays polymorphism which is controlled by the active substance manufacturer.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The active substance is manufactured in five steps from the starting material. In the final step the other starting material is added. No class I solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. It also includes additional requirements for the polymorphic form and residual ethanol Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No changes are seen under any condition. Based on the data submitted, a retest period could be granted of five years.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified.

A bioequivalence study has been performed versus the reference product. The test product batch of the highest strength used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process. Comparative dissolution studies at three pHs with the innovator product as well as the lower strength have generally been adequately performed to support the bioequivalence study and the biowaiver of additional strength respectively. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The orodispersible tablets are manufactured by a direct compression process which consists of sieving, lubrication and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented two full scaled 5 mg and three full scaled 10 mg batches. The product is manufactured using conventional manufacturing techniques. Process validation for three full scaled batches of both strengths will be completed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, disintegration, water content, dissolution, uniformity of dosage units, identification, assay, related substances and microbial contamination. The release and shelf-life limits are almost identical, except those for a specified impurity and total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from two full scaled 5 mg and three full scaled 10 mg batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for two full scaled 5 mg and three full scaled 10 mg batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light.

Under the 40°C/75% RH accelerated conditions the level of a specified impurity increases to above the acceptance limit. Under the 30°C/65% RH intermediate and 25°C/60% RH long term conditions the observed increase in this specified impurity remains within the acceptance limit. All other parameters remain stable. The proposed shelf-life of three years is justified, the proposed storage condition 'Do not store above 30°C. Store in the original package to protect from light and moisture.' is also justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rizatriptan Passauer has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rizatriptan Passauer is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Maxalt Smelt which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology,

pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rizatriptan benzoate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Rizatriptan Passauer 10 mg orodispersible tablet (Laboratorios Lesvi S.L., Spain) is compared with the pharmacokinetic profile of the reference product Maxalt Max 10 mg lyophilisates (MSD, Spain).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver is granted for the 5 mg strength as all the following criteria are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for all strengths.
- *In vitro* dissolution data between the 5 mg and 10 mg biobatch at a pH of 1.2, 4.5 and 6.8 showing comparable dissolution have been submitted.

Bioequivalence studies
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male (n=20) and female (n=10) subjects, aged 20-32 years. Each subject received a single dose (10 mg) of one of the two rizatriptan formulations. Before administration, subjects swallowed 20 ml plain water in order to wet their mouth. The formulation was then placed on the tongue and the

subject was asked to allow the tablet to orally dissolve and not to chew until completely disintegrated. The resulting suspension was swallowed. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.50, 2.75, 3, 4, 6, 8, 10, 12 and 24 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions has been applied, which is in accordance with the SmPC. Furthermore the administration procedure is acceptable, considering the formulation being an orodispersible tablet or lyophilisate which should be dissolve on the tongue before swallowing without water.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew after Period I for personal reasons. Therefore, 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of rizatriptan under fasted conditions.

Treatment N=39	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	76.9 ± 25.8	78.2 ± 26.0	26.9 ± 11.4	1.00 (0.25 – 3.0)	1.92 ± 0.34
Reference	75.5 ± 22.2	76.8 ± 22.7	25.9 ± 9.5	1.0 (0.50 – 2.50)	1.90 ± 0.28
***Ratio (90% CI)**	1.01 (0.97 – 1.04)	--	1.01 (0.92 – 1.10)	--	--
CV (%)	9.2	--	23.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Rizatriptan Passauer is considered bioequivalent with Maxalt Max.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rizatriptan Passauer.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Myocardial ischaemia infarction • Cerebrovascular events • Peripheral vascular events • Hypersensitivity • Concomitant use with SSRIs • Concomitant use with MAO inhibitors • Concomitant use with ergot–containing compounds • Concomitant use with beta-blockers • Medication overuse headache (MOH)
Important potential risks	• Use in patients with basilar or hemiplegic migraine • Blindness and significant partial vision loss (transient and permanent)
Missing information	• Use during pregnancy • Use during lactation • Use in patients with severe hepatic insufficiency • Use in patients with severe renal insufficiency • Use in patients with moderately severe or severe hypertension, or untreated mild hypertension • Use in children <18 years of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Maxalt Smelt. No new clinical studies were conducted. The MAH

demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zolmitriptan Invent Farma 5 mg orodispersible tablets from Spain. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rizatriptan Passauer 5 mg and 10 mg orodispersible tablets has a proven chemical-pharmaceutical quality and is a generic form of Maxalt Smelt. Maxalt Smelt is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rizatriptan Passauer with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 1 November 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse