IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Rizadia 5 mg oral lyophilisate
Rizatriptan benzoate
PA23198/027/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Rizadia 5mg oral lyophilisate, from Diapharm GmbH & Co. KG on 10th May 2024 indicated for use in adults for the acute treatment of the headache phase of migraine attacks with or without aura.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Rizatriptan MSD 5mg Oral lyophilisates, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Rizadia 5 mg oral lyophilisate. Rizadia 5 mg oral lyophilisate has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Rizatriptan MSD 5mg Oral lyophilisates.

Ireland acted as Reference Member State in this decentralised procedure. Germany was a Concerned Member State.

Rizadia 5 mg oral lyophilisate is a prescription-only medicinal product in Ireland.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Rizadia 5 mg oral lyophilizate
Name(s) of the active substance(s) (INN)	Rizatriptan benzoate
Pharmacotherapeutic classification (ATC code)	N02CC04
Pharmaceutical form and strength(s)	5 mg oral lyophilizate
Marketing Authorisation Number(s) in Ireland (PA)	PA23198/027/001
Marketing Authorisation Holder	Organon Pharma (Ireland) Limited
MRP/DCP No.	IE/H/1262/001-002/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Rizadia 5 mg oral lyophilisate.

II.2 Drug substance

The active substance is rizatriptan benzoate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each oral lyophilisate contains 7.265 mg of rizatriptan benzoate (corresponding to 5 mg of rizatriptan).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form. Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizatriptan MSD 5 mg oral lyophilisate, which has been considered assessed and authorised.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizadia, which has been considered assessed and authorised.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizadia, which has been considered assessed and authorised.

P.5 Control of Finished Product

Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizadia, which has been considered assessed and authorised.

P.6 Packaging material

Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizadia, which has been considered assessed and authorised.

P.7 Stability of the Finished Product

The proposed shelf life of 3 years with 'Do not store above 30°C. Store in the original packaging in order to protect from moisture.' as storage conditions for the drug product, are in line with the reference product. Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizadia, which has been considered assessed and authorised.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

Reference is made to the up-to-date chemical-pharmaceutical documentation of the original dossier for Rizadia, which has been considered assessed and authorised.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Maxalt 5mg Oral Lyophilisates on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Rizatriptan is not a PBT substance as log Kow does not exceed 4.5. Rizatriptan PEC surface water value is above the action limit of 0.01 µg/L and a Phase II-Tier A environmental effect assessment and concomitant risk assessment was conducted. However, the PEC/PNEC ratio for surface water, ground water, microorganisms and sediment-dwelling organisms is less than one. Considering the above data, rizatriptan is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

This is an application under Article 10c of Directive 2001/83/EC (informed consent), as such the Nonclinical pharmacodynamic, pharmacokinetic and toxicological data are identical to Maxalt 5mg Oral Lyophilisates which has been assessed and approved.

IV. CLINICAL ASPECTS

IV.1 Introduction

Rizatriptan benzoate is a well-known active substance with an established efficacy and safety profile. This medicinal product is the same as Rizatriptan MSD 5 mg oral lyophilisate on the European market.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Rizatriptan MSD 5 mg oral lyophilisate marketed by Organon Pharma (Ireland) Limited.

IV.2 Pharmacokinetics

Absorption
Rizatriptan is rapidly and completely absorbed following oral administration. The mean oral bioavailability of the oral lyophilisate is approximately 40 – 45 %, and mean peak plasma concentrations (Cmax) are reached in approximately 1.58 hours (Tmax). The time to maximum plasma concentration following administration of rizatriptan as the oral lyophilisate formulation is delayed by 30 – 60 minutes relative to the tablet.

Effect of Food: The effect of food on the absorption of rizatriptan from the oral lyophilisate has not been studied. For the rizatriptan tablets, Tmax is delayed by approximately 1 hour when the tablets are administered in the fed state. A further delay in the absorption of rizatriptan may occur when the oral lyophilisate is administered after meals.

Distribution
Rizatriptan is minimally bound (14 %) to plasma proteins. The volume of distribution is approximately 140 litres in male subjects, and 110 litres in female subjects.

Biotransformation
The primary route of rizatriptan metabolism is via oxidative deamination by monoamine oxidase-A (MAO-A) to the indole acetic acid metabolite, which is not pharmacologically active. N-monodesmethyl-rizatriptan, a metabolite with activity similar to that of parent compound at the 5-HT1B/1D receptors, is formed to a minor degree, but does not contribute significantly to the pharmacodynamic activity of rizatriptan. Plasma concentrations of N-monodesmethyl-rizatriptan are approximately 14 % of those of parent compound, and it is eliminated at a similar rate. Other minor metabolites include the N-oxide, the 6-hydroxy compound, and the sulfate conjugate of the 6-hydroxy metabolite. None of these minor metabolites is pharmacologically active. Following oral administration of 14C-labeled rizatriptan, rizatriptan accounts for about 17 % of circulating plasma radioactivity.

Elimination
Following intravenous administration, AUC in men increases proportionally and in women near-proportionally with the dose over a dose range of 10 – 60 µg/kg. Following oral administration, AUC increases near-proportionally with the dose over a dose range of 2.5 - 10 mg. The plasma half-life of rizatriptan in males and females averages 2-3 hours. The plasma clearance of rizatriptan averages about 1,000 - 1,500 mL/min in males and about 900-1,100 mL/min in females; about 20-30 % of this is renal clearance. Following an oral dose of 14C-labeled rizatriptan, about 80 % of the radioactivity is excreted in urine, and about 10 % of the dose is excreted in faeces. This shows that the metabolites are excreted primarily via the kidneys.

Consistent with its first pass metabolism, approximately 14 % of an oral dose is excreted in urine as unchanged rizatriptan while 51 % is excreted as indole acetic acid metabolite. No more than 1 % is excreted in urine as the active N-monodesmethyl metabolite.

If rizatriptan is administered according to the maximum dosage regimen, no drug accumulation in the plasma occurs from day to day.

Characteristics in Patients
The following data are based on studies with the oral tablet formulation.

Patients with a migraine attack: A migraine attack does not affect the pharmacokinetics of rizatriptan.

Gender: The AUC of rizatriptan (10 mg orally) was about 25 % lower in males as compared to females, Cmax was 11 % lower, and Tmax occurred at approximately the same time. This apparent pharmacokinetic difference was of no clinical significance.

Elderly: The plasma concentrations of rizatriptan observed in elderly subjects (age range 65 to 77 years) after tablet administration were similar to those observed in young adults.

Paediatric population: A pharmacokinetics study of rizatriptan (as the oral lyophilisates formulation) was conducted in paediatric migraineurs 6 to 17 years of age. The mean exposures following a single dose administration of 5 mg rizatriptan oral lyophilisates to paediatric patients weighing 20 39 kg or 10 mg rizatriptan oral lyophilisates to paediatric patients weighing ≥40 kg were respectively 15 % lower and 17 % higher compared to the exposure observed following single dose administration of 10 mg rizatriptan oral lyophilisates to adults. The clinical relevance of these differences is unclear.

Hepatic impairment (Child-Pugh's score 5-6): Following oral tablet administration in patients with hepatic impairment caused by mild alcoholic cirrhosis of the liver, plasma concentrations of rizatriptan were similar to those seen in young male and female subjects. A significant increase in AUC (50 %) and Cmax (25 %) was observed in patients with moderate hepatic impairment (Child-Pugh's score 7). Pharmacokinetics were not studied in patients with Child-Pugh's score >7 (severe hepatic impairment).

Renal impairment: In patients with renal impairment (creatinine clearance 10 – 60 mL/min/1.73 m2), the AUC of rizatriptan after tablet administration was not significantly different from that in healthy subjects. In haemodialysis patients (creatinine clearance <10 mL/min/1.73 m2), the AUC for rizatriptan was approximately 44 % greater than that in patients with normal renal function. The maximal plasma concentration of rizatriptan in patients with all degrees of renal impairment was similar to that in healthy subjects.

IV.3 Pharmacodynamics

Pharmacotherapeutic group:
antimigraine preparations, selective serotonin (5HT1) agonists
ATC-code: N02C C04

Mechanism of action:
Selective serotonin (5HT $_{1B/1D}$) agonists

Rizatriptan binds selectively with high affinity to human 5-HT_{1B} and 5-HT_{1D} receptors and has little or no effect or pharmacological activity at 5-HT_2, 5-HT_3; adrenergic $alpha_1$, $alpha_2$ or beta; D_1, D_2, dopaminergic, histaminic H_1; muscarinic; or benzodiazepine receptors.

The therapeutic activity of rizatriptan in treating migraine headache may be attributed to its agonist effects at 5-HT_{1B} and 5-HT_{1D} 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-HT_{1B} and 5-HT_{1D} 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.

IV.4 Clinical Efficacy

As this is an informed consent application no new clinical efficacy data has been submitted. Efficacy is expected to be similar to the reference product Rizatriptan MSD 5 mg oral lyophilisate.

IV.5 Clinical Safety

As this is an informed consent application on new clinical safety data has been submitted. Safety is expected to be similar to the reference medicinal product Rizatriptan MSD 5 mg oral lyophilisate. The safety information in the SmPC and Package Leaflet are in line with those of the reference medicinal product.

Risk Management Plan

A Risk Management Plan, version 0.2, dated 25 September 2023 has been submitted, 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 benzoate. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Rizatriptan benzoate is a well-known active substance and has been widely marketed.

Rizadia 5 mg oral lyophilisate is an Informed Consent form of Rizatriptan MSD 5 mg oral lyophilisate which is a well-known medicinal product approved in Europe for the treatment of the headache phase of migraine attacks with or without aura in adults, which has a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Rizadia 5 mg oral lyophilisate is a prescription-only medicinal product in Ireland.

The content of the SmPC approved during this decentralised procedure is aligned with the reference product Rizatriptan MSD 5 mg oral lyophilisate.

V. OVERALL CONCLUSIONS

Rizadia 5 mg oral lyophilisate is the same as Rizatriptan MSD 5 mg oral lyophilisate. Rizatriptan MSD 5 mg oral lyophilisate is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The MAH has provided written confirmation that the systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Rizadia 5 mg oral lyophilisate was the same as the reference product and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
N/A

VI. REVISION DATE

September 2024

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	**PROCEDURE NUMBER**	**PRODUCT INFORMATION AFFECTED**	**DATE OF START OF PROCEDURE**	**DATE OF END OF PROCEDURE**
New DCP as RMS	IE/H/1262/001/DC	SmPC, PAR	10th May 2024	9th May 2024
MA transfer	N/A	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Organon Pharma (Ireland) Limited New PA number: PA23198/027/001	N/A	06/09/2024