IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 Eletriptan Hormosan 20 mg and 40 mg film-coated tablets from Hormosan Pharma GmbH on 18th December 2020 for the acute treatment of the headache phase of migraine attacks, with or without aura, in adults.

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended and via the decentralised procedure, whereby Ireland (IE) was the Reference Member State and Germany (DE) was the only Concerned Member State.

The reference products, Relpax 20 mg and 40 mg film-coated tablets developed by Pfizer Italia S.r.l., have been authorised in the European Economic Area since January 2002.

The applicant's product, Eletriptan Hormosan 20 mg and 40 mg film-coated tablets are of the same indication, strength and route of administration as that of the reference medicinal product, Relpax 20 mg and 40 mg film-coated tablets.

Eletriptan Hormosan 20 mg and 40 mg film-coated tablets are subject to prescription, which may be renewed.

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 – Eletriptan Hormosan 20 mg film-coated tablets
Name(s) of the active substance(s) (INN) – Eletriptan
Pharmacotherapeutic classification (ATC code) – N02CC06
Pharmaceutical form and strength(s) – Film-coated tablet; 20 mg
Marketing Authorisation Number(s) in Ireland (PA) - PA23052/001/001
Marketing Authorisation Holder – Hormosan Pharma GmbH
MRP/DCP No. IE/H/1144/001
Reference Member State - IE
Concerned Member State – DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Eletriptan Hormosan 20 mg and 40 mg film-coated tablets.

II.2 Drug substance

The active substance is Eletriptan hydrobromide, an established active substance not 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. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product

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 and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

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

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The finished product specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Eletriptan 20 mg and 40 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Relpax 20 mg and 40 mg film-coated tablets 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 Ecotoxicity/environmental risk assessment

Since Eletriptan Hormosan 20 mg and 40 mg film-coated tablets are 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.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of eletriptan are well known. As eletriptan is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under Article 10(1) of Directive 2001/83/EC.

Eletriptan is a well-known active substance with established efficacy and tolerability.

The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the reference product Relpax 20 mg and 40 mg film-coated tablets marketed by Pfizer Italia S.r.l..

To support the application, the applicant has submitted the report of a bioequivalence study with the 40 mg strength and a justification for waiver of a bioequivalence study with the 20 mg strength.

Bioequivalence study: 40 mg strength
The applicant submitted a bioequivalence study in which the pharmacokinetic profile of the test product Eletriptan Hormosan 40 mg film-coated tablets was compared with the pharmacokinetic profile of the reference product Relpax 40 mg film-coated tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Eletriptan Hormosan 40 mg film-coated tablets was compared to the reference product Relpax 40 mg film-coated tablets. Based on the pharmacokinetic parameters of active substance eletriptan, the reference tablet Relpax 40 mg film-coated tablets and test product Eletriptan Hormosan 40 film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Biowaiver: 20 mg strength
A justification for waiver of a study with the 20 mg strength was provided in accordance with recommendations in the bioequivalence guideline:
- Both strengths are manufactured by the same manufacturer and process
- The qualitative composition of the two strengths are the same
- Composition of strengths are quantitatively proportional
- The dissolution profiles are comparable over the pH range 1 to 6.8 under appropriate conditions
- The pharmacokinetics is linear in the therapeutic dosage range

Based on the above, waiver of a bioequivalence study with the 20 mg strength is acceptable and the results of the bioequivalence study performed with the 40 mg film-coated tablets therefore apply to the 20 mg film-coated tablet strength.

IV.2 Pharmacokinetics

Absorption
Eletriptan is rapidly and well absorbed across the gastro-intestinal tract (at least 81%) after oral administration. Absolute oral bioavailability across males and females is approximately 50%. The median T_{max} is 1.5 hours after oral dosing. Linear pharmacokinetics were demonstrated over the clinical dose range (20-80 mg).
The AUC and C_{max} of eletriptan were increased by approximately 20-30% following oral administration with a high fat meal. Following oral administration during a migraine attack, there was a reduction of approximately 30% in AUC and T_{max} was increased to 2.8 hours.
Following repeated doses (20 mg three times daily) for 5-7 days, the pharmacokinetics of eletriptan remained linear and accumulation was predictable. On multiple dosing of larger doses (40 mg three times daily and 80 mg two times daily), the accumulation of eletriptan over 7 days was greater than predicted (approximately 40%).

Distribution
The volume of distribution of eletriptan following IV administration is 138L indicating distribution into the tissues. Eletriptan is only moderately protein bound (approximately 85%).

Biotransformation
In vitro studies indicate that eletriptan is primarily metabolised by hepatic cytochrome P-450 enzyme CYP3A4. This finding is substantiated by increased plasma concentrations of eletriptan following co-administration with erythromycin and ketoconazole, known selective and potent CYP3A4 inhibitors. *In vitro* studies also indicate a small involvement of CYP2D6 although clinical studies do not indicate any evidence of polymorphism with this enzyme.
There are two major circulating metabolites identified that significantly contribute to plasma radioactivity following administration of C14-labelled eletriptan. The metabolite formed by
N-oxidation, has demonstrated no activity in animal in vitro models. The metabolite formed by N-demethylation, has been demonstrated to have similar activity to eletriptan in animal in vitro models. A third area of radioactivity in plasma has not been formally identified, but is most likely to be a mixture of hydroxylated metabolites, which have also been observed excreted in urine and faeces.
The plasma concentrations of the N-demethylated active metabolite are only 10-20% of those of parent and so would not be expected to significantly contribute to the therapeutic action of eletriptan.

Elimination
Mean total plasma clearance of eletriptan following IV administration is 36 L/h with a resultant plasma half-life of approximately 4 hours. The mean renal clearance following oral administration is approximately 3.9 L/h. Non-renal clearance accounts for approximately 90% of the total clearance indicating that eletriptan is eliminated primarily by metabolism.

IV.3 Pharmacodynamics

Mechanism of action

Eletriptan is a selective agonist at the vascular 5-HT1B and neuronal 5-HT1D receptors.
Eletriptan also exhibits high affinity for the 5-HT1F receptor, which may contribute to its antimigraine mechanism of action.
Eletriptan has modest affinity for the human recombinant 5-HT1A, 5-HT2B, 5-HT1E and 5-HT7 receptors.

No new pharmacodynamic studies have been provided and none are required.

IV.4 Clinical Efficacy

The efficacy of eletriptan in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety

The overall safety profile of eletriptan is established and generally known. No new safety studies are provided and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

Risk Management Plan
The Applicant 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 Eletriptan Hormorsan 20mg and 40mg film coated tablet.
The submitted Risk Management Plan, version 0.1 signed 30th April 2020 is considered acceptable.
Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Safety specification

Safety concerns	
Important identified risks	• Cardiovascular events (including vascular disease and cardiac disease) • Serotonin syndrome following concomitant therapy with serotonergic agents • Hypersensitivity • Medication overuse headache

Important potential risks	• Ischaemic colitis • Use in pregnancy
Missing information	• Use in elderly population (>65 years of age) • Use in paediatric population (< 18 years of age) • Use in lactation

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.

Common renewal date
Common renewal date will be 5 years after the finalisation of the procedure.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.
The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test product Eletriptan Hormosan 40 mg film-coated tablets against the reference product Relpax 40 mg film-coated tablets, in accordance with the relevant guidance. A justification for waiver of a study with the 20 mg strength has been provided. No additional tests are required for this application.
The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Eletriptan Hormosan 20 mg and 40 mg film-coated tablets, from Hormosan Pharma GmbH, are generic forms of Relpax 20 mg and 40 mg film-coated tablets developed by Pfizer Italia S.r.l.. Relpax 20 mg and 40 mg film-coated tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considered that Eletriptan Hormosan 20 mg and 40 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.