IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Naratriptan
Naratriptan hydrochloride
PA22865/008/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Naratriptan 2.5 mg Film-coated tablet, from Renata Pharmaceuticals (Ireland) Limited on 10th May 2024 for the treatment of acute treatment of migraine attacks with or without aura.

This is a generic product and the legal basis for this application is article 10 (1) of Directive 2001/83/EC as amended.

HPRA was RMS in this decentralised procedure and Malta was a CMS.

This medicinal product is 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	Naratriptan 2.5 mg Film-coated tablet
Name(s) of the active substance(s) (INN)	Naratriptan
Pharmacotherapeutic classification (ATC code)	N02CC02
Pharmaceutical form and strength(s)	2.5 mg Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22865/008/001
Marketing Authorisation Holder	Renata Pharmaceuticals (Ireland) Limited
MRP/DCP No.	IE/H/1227/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Naratriptan 2.5 mg Film-coated tablet.

II.2 Drug substance

The active substance is Naratriptan, an established active substance, 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 film coated tablet contains 2.5 mg of naratriptan (as naratriptan hydrochloride)

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 suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH 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 the dosage form, 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(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 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 Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 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, Pharmaceutical and Biological 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 Naratriptan 2.5 mg film coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Naramig 2.5 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 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Naratriptan 2.5 mg film-coated tablet is intended for generic substitution, an increased environmental exposure is not anticipated. Environmental risk assessment studies are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of naratriptan are well known. As naratriptan is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Naramig 2.5 mg film coated tablets marketed by GlaxoSmithKline GmbH & Co. KG, registered in Germany since 1/8/1997, [40706.00.00]. This registration was based on a full dossier submission in a mutual recognition procedure SE/H/0131/001.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Naratriptan 2.5 mg film coated tablets is compared with the pharmacokinetic profile of the reference product Naramig 2.5 mg film coated tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Naratriptan 2.5 mg film coated tablets, Renata Pharmaceuticals (Ireland) Limited was compared to the reference product Naramig 2.5 mg film coated tablets, GlaxoSmithKline GmbH & Co. KG. Based on the pharmacokinetic parameters of active substance, the reference tablet Naramig 2.5 mg film coated tablets marketed by GlaxoSmithKline GmbH & Co. KG, and test tablet Naratriptan 2.5 mg 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.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
Following oral administration of naratriptan, maximum plasma concentrations are observed after 2-3 hours. After intake of one 2.5 mg naratriptan tablet, C_{max} is approximately 8.3 ng/ml (95% CI: 6.5 to 10.5 ng/ml) in women and 5.4 ng/ml (95% CI: 4.7 to 6.1 ng/ml) in men.
The oral bioavailability is 74% in women and 63% in men with no differences in efficacy and tolerability in clinical use. Therefore, a gender-related dose adjustment is not required.

Distribution
Naratriptan is distributed in a volume of 170L. Plasma protein binding is low (29%).

Biotransformation
Mean clearance after intravenous administration was 470 ml/min in men and 380 ml/min in women. Renal clearance is similar in men and women at 220 ml/min and is higher than the glomerular filtration rate suggesting that naratriptan is actively secreted in the renal tubules. Naratriptan is predominantly excreted in the urine with 50% of the dose recovered as unchanged naratriptan and 30% recovered as inactive metabolites. In vitro, naratriptan is metabolised by a wide range of cytochrome P450 isoenzymes. Consequently, significant metabolic interactions with naratriptan are not anticipated.

Naratriptan does not inhibit P450 enzymes. Whether naratriptan has inducing potential with respect to human isoenzymes is unknown, however, no significant changes in the expression of hepatic cytochrome P450 isoforms were observed in rats.

Elimination
The mean elimination half-life ($t_{1/2}$) is 6 hours.

Special Patient Populations

Elderly
In healthy elderly subjects (n=12), clearance was decreased by 26% and AUC was increased by 30% when compared to healthy young subjects (n=12) in the same study.

Gender
The naratriptan AUC and C_{max} were approximately 35% lower in males compared to females, possibly due to the co-administration of oral contraceptives. However, there were no differences in efficacy and tolerability in clinical use. Therefore a gender-related dose adjustment is not required.

Renal impairment
Renal excretion is the major route for the elimination of naratriptan. Accordingly exposure to naratriptan may be increased in patients with renal disease. In a study in male and female patients with renal impairment (creatinine clearance 18 to 115 ml/min; n=15) matched for sex, age and weight with healthy subjects (n=8), patients with renal impairment had an approximately 80% increase in $t_{1/2}$ and an approximately 50% reduction in clearance.

Hepatic impairment
The liver plays a lesser role in the clearance of orally administered naratriptan. In a study in male and female patients with hepatic impairment (Child-Pugh grade A or B; n=8) who were matched for sex, age and weight with healthy subjects who received oral naratriptan, patients with hepatic impairment had an approximately 40% increase in $t_{1/2}$ and an approximately 30% reduction in clearance.

IV.3 Pharmacodynamics

Mechanism of action
Naratriptan has been shown to be a selective agonist for 5 hydroxytryptamine1 (5-HT_1) receptors mediating vascular contraction. Naratriptan has high affinity for human cloned 5-HT_{1B} and 5-HT_{1D} receptors, the human 5-HT_{1B} receptor is thought to correspond to the vascular 5-HT_1 receptor mediating contraction of intracranial blood vessels. Naratriptan has little or no effect on other 5- HT receptor (5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7) subtypes.

In animals, naratriptan selectively constricts the carotid arterial circulation. In addition, experimental studies in animal suggest that naratriptan inhibits trigeminal nerve activity. Both these actions may contribute to the anti-migraine action of naratriptan in humans.

IV.4 Clinical Efficacy

No clinical efficacy data are provided as this is a generic application.

IV.5 Clinical Safety

As this is a generic application, no other clinical safety data are required.

Risk Management Plan (RMP)
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 Naratriptan 2.5 mg Film-coated tablet.

Safety specification

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

Pharmacovigilance activities

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

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

As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products.

V. OVERALL CONCLUSIONS

Naratriptan 2.5 mg film coated tablets is a generic form of Naramig 2.5 mg film coated tablets. Naramig 2.5 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 Naratriptan 2.5 mg film coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

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/1227/001/DC	SPC, IPAR	10th May 2024	9th May 2029