IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ondansetron 4 mg/5 ml syrup
Ondansetron
PA22697/013/001

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 Ondansetron 4 mg/5 ml syrup, from Syri Pharma Limited t/a Thame Laboratories for the following indications:

Ondansetron 4 mg/5 ml syrup is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Ondansetron 4 mg/5 ml syrup is also indicated for the prevention of post-operative nausea and vomiting (PONV).
For treatment of established PONV, administration by injection is recommended.

The legal basis of this application is in accordance with Article 10(1) of Directive 2001/83/EC. The European reference medicinal product is Zofran 4mg/5ml Syrup (PA0896/036/003) from Novartis Ireland Limited.

Ondansetron 4 mg/5 ml syrup was initially authorised in the UK (Reference Member State) and Ireland (Concerned Member State) via decentralised procedure UK/H/5721/001/DC which concluded on 05/03/2015.

Ireland took over as Reference Member State (RMS) in 2019.

Netherlands was added as Concerned Member State (CMS) via mutual Recognition Procedure IE/H/0779/001/E/001 in November 2021.

The product is subject to prescription 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	Ondansetron 4 mg/5 ml syrup
Name(s) of the active substance(s) (INN)	Ondansetron
Pharmacotherapeutic classification (ATC code)	A04AA01
Pharmaceutical form and strength(s)	4 mg/5 ml syrup
Marketing Authorisation Number(s) in Ireland (PA)	PA22697/013/001
Marketing Authorisation Holder	Syri Pharma Limited t/a Thame Laboratories
MRP/DCP No.	IE/H/0779/001/E/001
Reference Member State	IE
Concerned Member State	NL

I INTRODUCTION

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ondansetron 4 mg/5 ml syrup.

II.2 Drug substance

The active substance is Ondansetron, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP). The EDQM CEP procedure is used.

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

Ondansetron 4 mg/5 ml syrup is clear, colourless syrup with strawberry flavour. The other ingredients in the product are Citric acid monohydrate (E330), Sodium citrate (E331), Sorbitol, liquid (non-crystallising) (E420), Sodium benzoate (E211), Strawberry flavour (contains propylene glycol (E1520)) and Purified water.

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
A description and flow-chart of the manufacturing method has been provided and is satisfactory.
In-process controls are appropriate considering the nature of the product and the method of manufacture. The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing site.
The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)
All excipients used in the drug product with the exception of strawberry flavour are described in the Eurpean pharmacopoeia and comply with their respective monographs. Strawberry flavour is the subject of an in-house specification and is adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for Liquid preparations for oral use 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. requirements and 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 Ondansetron 4 mg/5 ml syrup.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Zofran 4mg/5ml Syrup (PA0896/036/003) 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 Ondansetron 4 mg/5 ml syrup is a generic product, it will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron are well known. As ondansetron is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of application. Nonclinical sections of the SmPC are in line with the originator which is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the MR procedure is essentially the same as that accepted for the reference product Zofran 4mg/5ml Syrup (PA0896/036/003) marketed by Novartis Ireland Limited.

A bioequivalence study was not performed as it satisfies the criteria for a biowaiver in accordance with the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

IV.2 Pharmacokinetics

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30ng/mL are attained approximately 1.5 hours after an 8mg dose. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. The disposition of ondansetron following oral, intramuscular(IM) and intravenous(IV) dosing is similar with a terminal half-life of about 3 hours and steady state volume of distribution of about 140L.

IV.3 Pharmacodynamics

ATC code: A04AA01,
Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonist

Mechanism of Action
Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known.

IV.4 Clinical Efficacy

The clinical efficacy of ondansetron is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The clinical safety of ondansetron is well established. No additional safety clinical studies to demonstrate safety have been included in the application. This is appropriate for this type of application.

Risk Management Plan

The product has a Risk Management Plan (version 2.1 dated 13th February 2017). The risk management plan including the proposed routine pharmacovigilance activities and routine risk minimisation measures is considered acceptable.
The approved summary of safety concerns is outlined in the table below:

Summary of safety concerns	
Important identified risks	• QT interval prolongation and Torsades de Pointes
Important potential risks	• Inadvertent overdose due to medication error leading to serotonin syndrome in infants and children aged 12 months to 2 years
Missing information	• None

Pharmacovigilance System
The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Periodic Safety Update Reports (PSURs)
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 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.
A bioequivalence study was not performed as it satisfies the criteria for a biowaiver in accordance with the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.
The benefit/risk profile of the product is considered to be positive.

V. OVERALL CONCLUSIONS

Ondansetron 4 mg/5 ml syrup is a generic form of Zofran 4mg/5ml Syrup (PA0896/036/003). Zofran 4mg/5ml Syrup (PA0896/036/003) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

A bioequivalence study was not performed as it satisfies the criteria for a biowaiver in accordance with the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

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 Ondansetron 4 mg/5 ml syrup demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

The marketing authorisaton has been granted unlimited validity in the RMS.