IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ondansetron 2mg/ml Solution for Injection
Ondansetron
PA2299/037/001

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

This product was initially authorised under procedure number UK/H/1240/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 05/12/2018 under procedure number IE/H/0865/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2299/037/001
Marketing Authorisation Holder: Baxter Holding BV

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Belgium, Estonia, Germany, Greece, Ireland, Italy, Lithuania, Luxemburg, Latvia, The Netherlands, Poland, Portugal, Slovenia and the UK considered that the application for Ondansetron 2mg/ml Solution for Injection could be approved. This prescription only medicine (POM) is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of post-operative nausea and vomiting (PONV).

This application for Ondansetron 2mg/ml Solution for Injection is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Zofran 2mg/ml Solution for Injection, first authorised in the UK to Glaxo Smithkline UK in March 1990.

The product contains the active substance ondansetron (as hydrochloride dihydrate), a selective inhibitor of type 3 serotonin (5-hydroxytryptamine) receptors (5-HT_3) that exhibits anti-emetic activity, although the exact mechanism of action is not known.

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of ondansetron hydrochloride dihydrate is well-established. No clinical pharmacology data is required for this generic injection solution.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. QUALITY ASPECTS

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Name: Ondansetron hydrochloride dehydrate

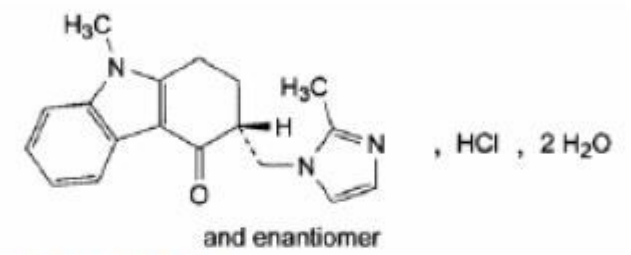
INN/Ph.Eur name: Ondansetron

Chemical name: (RS)-1,2,3,9-Tetrahydro-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

(3RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one hydrochloride dehydrate

(RS)-1,2,3,9-Tetrahydro-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]carbazone-4-one

Structural formula:



Molecular formula: $C_{18}H_{20}C1N_3O,2H_2O$

Appearance: A white to off-white powder.
It is sparingly soluble in water and alcohol; soluble in methanol and slightly soluble in methylene chloride.

Molecular weight: 365.9

Ondansetron hydrochloride dihydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance ondansetron hydrochloride dihydrate from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance ondansetron hydrochloride dihydrate.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients citric acid monohydrate, sodium citrate, sodium chloride and water for injections.

All excipients comply with their European Pharmacopoeia monograph.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Zofran 2mg/ml Solution for Injection (Glaxo Smithkline UK, March 1990).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Zofran 2mg/ml Solution for Injection (Glaxo Smithkline UK).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The applicant has committed to perform process validation with production-scale batches of the drug product.

Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working reference standards used.

Container-Closure System

The product is packaged in ampoules composed of type I clear glass.
Specifications and certificates of analysis for the packaging used have been provided. The product is packaged in sizes of 2ml and 5ml ampoules, containing 2ml and 4ml of solution, respectively.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

Stability of the product

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of three years for an unopened product with storage conditions "Keep the ampoules in the outer carton in order to protect from light."

Regarding the shelf-life of the injection "Once opened, the product should be used immediately"

Storage conditions for the infusion are "Chemical and physical in-use stability has been demonstrated for 36 hours at 2-8°C".

General storage conditions for the product are "From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions."

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a marketing authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of ondansetron hydrochloride dihydrate are well-known. As ondansetron hydrochloride dihydrate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

No bioequivalence studies have been performed and none are required for this application, as the applicant's product is similar to the reference product in terms of qualitative and quantitative composition and is expected to perform identically *in vivo*. A human bioavailability study is not relevant to this application as the compound is intended for intravenous infusion.

3. Post marketing experience

Ondansetron hydrochloride dihydrate has a well-recognised efficacy and an acceptable level of safety in the indications approved for Zofran 2mg/ml Solution for Injection, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. Benefit-Risk assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with ondansetron hydrochloride dihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of a marketing authorisation for Ondansetron 2mg/ml Solution for Injection is recommended from a clinical viewpoint.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 2mg/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

CLINICAL

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ondansetron hydrochloride dihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

VI. REVISION DATE

25/02/2022

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
RMS transfer	From UK/H/1240/1/DC to IE/H/0865/1/DC			