COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ondansetron Accord 4 mg and 8 mg solution for injection/infusion in pre-filled syringe (ondansetron hydrochloride dihydrate)

NL/H/6471/001-002/DC

Date: 20 August 2025

This module reflects the scientific discussion for the approval of Ondansetron Accord 4 mg and 8 mg solution for injection/infusion in pre-filled syringe. The procedure was finalised at 25 February 2020 in Spain (ES/H/0627/001-002/DC) After a transfer on 18 July 2025, the current RMS is the Netherlands. For information on changes after the finalisation date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ondansetron Accord 4 mg and 8 mg solution for injection/infusion, from Accord Healthcare B.V.

The product is indicated for:

Adults:
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy,
Prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Management of chemotherapy-induced nausea and vomiting in children aged ≥6 months.
No studies have been conducted on the use of orally administered ondansetron in the prevention and treatment of PONV. For prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month i.v. injection is recommended.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article Art 10(3) – hybrid application of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as solution for injection/infusion in pre-filled syringe containing 2 mg and 4 mg of the active substance ondasentron (as ondansentron hydrochloride dihydrate). The concentration of the solution, 2 mg/mL, is the same for both strengths and they differ in the volume of solution in the syringe (2 mL and 4 mL). The maximum daily dose is 32 mg of ondansentron.

The product is available in type I amber glass prefilled syringe.

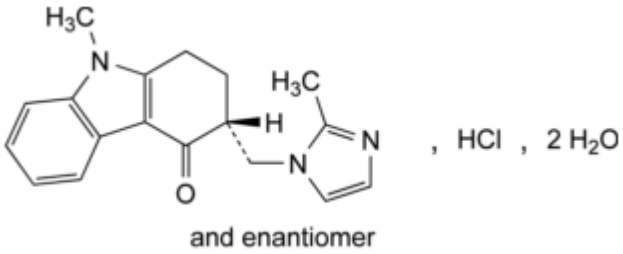
II.2 Drug Substance

The CEP procedure has been used to support the quality of the active substance.

General Information
Nomenclature:

INN:	Ondansetron
Chemical name:	(3RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9 tetrahydro-4H-carbazol-4-one hydrochloride dihydrate
CAS-No:	103639-04-9

Structure:



General Properties:
White or almost white powder, sparingly soluble in water, soluble in methanol, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

Manufacturing process
As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Quality control of drug substance
Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included

Container closure system
As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability of drug substance
Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

II.3 Medicinal Product

The finished product is presented as a solution for injection/infusion in pre-filled syringe containing 2 mg and 4 mg of the active substance ondasentron (as ondansentron hydrochloride dihydrate). The concentration of the solution, 2 mg/mL, is the same for both strengths and they differ in the volume of solution in the syringe (2 mL and 4 mL). The maximum daily dose is 32 mg of ondansentron. The other components of the medicinla product are sodium citrate, sodium chloride, sodium hydroxide/hydrochloric acid (for pH adjusting) and water for injection.

The product is available in type I amber glass prefilled syringe.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

The proposed method of sterilization has been appropriately justified.

Manufacturing process
The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Control of excipients
Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.

Quality control of drug product
The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system
The finished product is packaged in type I amber glass prefilled syringes. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability of drug product
Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life:	3 years.
Storage conditions:	Does not require special storage conditions.
In-use shelf life:	Use immediately after opening.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ondansetron 4 mg and 8 mg solution for injection/infusion in pre-filled syringe is intended for generic substitution, this will not lead to an increased exposure to the environment and therefore, additional ERA studies are not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic 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 additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known.
Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex.
Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.
The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

The Applicant did not conduct any clinical study to support this application.

IV.2 Pharmacokinetics

Clinical bioequivalence studies were not considered necessary in view of the fact that both the reference product and the proposed product were aqueous parenteral solutions containing the same active substance as the approved product.

Biowaiver
The qualitative composition was described in table below:

Components	Ondansetron Accord mg/mL	Zofran® mg/mL
Active Substance		
Ondansetron Hydrochloride Dihydrate Ondansetron Hydrochloride e.q to Ondansetron base	2.49 2.25 2.00	2.00
Excipients		
Sodium chloride	9.00	V
Citric acid monohydrate	0.50	V
Sodium citrate dihydrate	0.25	V
Sodium Hydroxide	q.s. to pH adjustment	-
Hydrochloric acid Concentrated	q.s. to pH adjustment	-
Water for injections	q.s. to 1.0 mL	V

According to the Guideline on the Investigation of Bioequivalence, a bioequivalence study was not required for an aqueous parenteral solution with similar excipients in similar amounts. The applied product also contained qualitatively the same excipients in similar amounts as the reference product, with the exception of sodium hydroxide and hydrochloric acid, which were used as pH-adjusting agents. The quantitative differences were not expected to affect the bioavailability between the two products.

IV.3 Pharmacodynamics

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

Absorption
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 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.
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.
A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

Distribution
The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing in adults is similar with a terminal half-life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. Ondansetron is not highly protein bound (70-76%).

Elimination
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

IV.4 Clinical efficacy and safety

The efficacy and safety of the active substance ondansetron (as ondansetron hydrochloride dihydrate) are well established and documented for the reference medicinal product.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan (version 1.1 signed 31 August 2019), 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 Ondansetron Accord 4 mg and 8 mg solution for injection/infusion in pre-filled syringe.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity • QT interval prolongation and Torsade de Pointes • Profound hypotension and loss of consciousness when administered with apomorphine hydrochloride • Toxic skin eruption, including Toxic Epidermal Necrolysis (TEN)
Important potential risks	• Serotonin syndrome • Adverse birth outcome following use during pregnancy • Reduced clearance and prolonged half-life in patients with hepatic impairment • Sub-acute intestinal obstruction in patients with impaired gastrointestinal motility • Adverse events in breast-fed infants due to use of ondansetron during lactation
Missing information	• Safety in pregnant women

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned Ondansetron Accord 4 mg and 8 mg solution for injection/infusion in pre-filled syringe.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to:
- Parent PIL-1 = Zofran Injection 2 mg/ml, 2 ml & 4 ml
- Parent PIL-2 = Ondnansetron 2 mg/ml Solution for injection
- Daughter PIL = Ondansetron 4 mg and 8 mg solution for injection/infusion in pre-filled syringe

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of for Ondansetron Accord 4 mg and 8 mg solution for injection/infusion in prefilled syringe is considered adequate, there are no objections to the approval of this medicinal product from a non-clinical and clinical point of view.

The efficacy and safety of the active substance for Ondansetron, have been sufficiently demonstrated.

The product information is acceptable. The benefit/risk ratio is considered positive and therefore authorisation is recommended.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
ES/H/0627/001-2/IB/001	Change in the (invented) name of the medicinal product for Nationally Authorised Products	Yes	6-11-2020	Approved	N.A.
ES/H/0627/001-2/IA/002	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) • Change that affects the product information	Yes	20-11-2020	Not approved	Not available
ES/H/0627/001-2/IB/003/G	Change in shape or dimensions of the container or closure (immediate packaging) • Sterile medicinal products Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) • Change that affects the product information	No Yes	28-5-2021	Approved	N.A.
ES/H/0627/001-2/II/004	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/ hybrid/biosimilar medicinal products following assessment of the same change for the reference product	Yes	11-1-2022	Approved	N.A.

	• Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)				
ES/H/0627/001-2/IA/005	Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release ○ Not including batch control/ testing	Yes	28-4-2021	Approved	N.A.
ES/H/0627/001-2/IB/006/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site • Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) manufactured	No	27-5-2022	Approved	N.A.

	using an aseptic method excluding biological/ immunological medicinal products Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product • Minor change in the manufacturing process Change in the batch size (including batch size ranges) of the finished product • Up to 10-fold compared to the originally approved batch size	 No No			
ES/H/0627/001 -2/IB/007	Change in the shelf-life or storage conditions of the finished product • Extension of the shelf life of the finished product ○ As packaged for sale (support- ed by real time data)	Yes	19-4-2022	Approved	N.A.
ES/H/0627/001 -2/IB/008/G	3 x Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product • Minor change in the manufacturing process.	No	27-6-2022	Approved	N.A.
ES/H/0627/001 -2/IB/009	Change to in-process tests or limits applied during the	No	27-6-2022	Approved	N.A.

	manufacture of the finished product • Other variation				
ES/H/0627/001-2/IB/010	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	6-10-2022	Refused	Not available
ES/H/0627/001-2/IA/011	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).	No	21-12-2022	Approved	N.A.
ES/H/0627/001-2/II/012	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)	Yes	17-2-2023	Approved	N.A.
ES/H/0627/001-2/II/013	Change(s) in the Summary of Product Characteristics,	Yes	18-6-2024	Approved	N.A.

	Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product • Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)				
ES/H/0627/001-2/R/001	Renewal	No	9-7-2024	Approved	N.A.
ES/H/0627/001-2/IA/014	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).	Yes	2-8-2024	Approved	N.A.
ES/H/0627/001-2/IA/015/G	2 x Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • All other: The activities for which the manufacturer/importer is responsible do not include batch release Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or	No No	24-1-2025	Approved	N.A.

	addition of a site where batch control/testing takes place				
ES/H/0627/001-2/IA/016/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a manufacturer responsible for importation and/or batch release ○ Including batch control/ testing	No Yes	7-3-2025	Approved	N.A.