CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Ondansetron STADA 4 mg, 8 mg orodispersible tablets
LT/H/0209/001-002/DC

Ondansetron STADA Arzneimittel AG 4 mg, 8 mg orodispersible tablets
LT/H/0228/001-002/DC

Date: 18 June 2025

This module reflects the scientific discussion for the approval of Ondansetron 4 mg, 8 mg orodispersible tablets. The procedure was finalised at 16 April, 2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ondansetron 4 mg, 8 mg orodispersible tablets.

The product is indicated to treat following indications:
Adults

- For the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting.

Peadiatric population

- For the management of chemotherapy-induced nausea and vomiting in children aged ≥ 6 months

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

The application is submitted in accordance with article 10(1) 'generic application' of Directive 2001/83/EC.
The concerned member states are Belgium, Luxembourg, Germany, Denmark, Finland, France, Iceland, Norway, Sweden.

II. QUALITY ASPECTS

II.1 Introduction

4 mg orodispersible tablets
Round, white to off-white, flat, bevelled edged, tablets plain on both sides, having a diameter of 8 mm ± 0.3 mm.

8 mg orodispersible tablets
Round, white to off-white, flat, bevelled edged, tablets plain on one side and "8" engraved on opposite side, having a diameter of 11 mm ± 0.3 mm.

The excipients are mannitol, colloidal anhydrous silica, basic butylated methacrylate copolymer, mannitol granular, crospovidone, aspartame, magnesium stearate.

Drug product is packed in Alu/Alu blister packs.

II.2 Drug Substance

The active substance is ondansetron, which is not included in the Ph. Eur and described in USP.

The ASMF procedure is used for the active substance.

Manufacturing process
Short synthetic scheme is provided, three synthesis steps are discussed.

Quality control of drug substance

The drug substance specification has been established in house by the Applicant. Provided specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the drug substance have been provided for four full scale batches stored at 25°C/60% RH (up to 72 months) and 40°C/75% RH (up to 6 months). The proposed retest period is 60 months.

II.3 Medicinal Product

Pharmaceutical development
The objective of the formulation development was to obtain a robust and stable formulation of ondansetron in the form of orodispersible tablets containing 4 mg or 8 mg of ondansetron comparable to that of the innovator Zofran Melt 8 mg oral lyophilisate.
The development of the product has been described; the choice of excipients was justified. The critical quality attributes of the formulation of drug product were identified.
The dissolution method, used for development studies is justified. Pharmaceutical equivalence between reference and test products is justified. The composition of the different strengths is dose proportional.

Manufacturing process
A flow chart of the manufacturing process and accompanying descriptive narrative are provided.
The manufacturing process is described and sufficiently validated. Manufacturing equipment is indicated only in general terms. The level of detail provided in the manufacturing process is deemed adequate. Information about critical steps of manufacturing process is provided.

Control of excipients
The excipients present in the drug product are indicated to be Ph. Eur. grade and therefore specifications have not been provided. This is accepted. Similarly, analytical procedures, method validation and justification of specifications are not required for Ph. Eur. excipients.
In-house specifications together with the analytical procedures are provided for non-compendial excipients.
There are no novel excipients used in the finished product formulation.

Quality control of drug product
A release and shelf-life specifications for both strengths are provided and include tests for description of the tablet, identification, assay, related substances, disintegration, dissolution, uniformity of dosage units, loss on drying, residual solvents, diameter and thickness, microbiological control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability studies are carried out under ICH conditions. The tested batches were stored in the intended packaging. The tested parameters are considered to indicate stability sufficiently. Data is available at long term (25°C/60%RH) and accelerated (40°C/75%RH) conditions. It is evident that the drug product in its commercial presentations is a stable product with no OOS results/obvious trends observed. All results met the proposed specifications. The provided

stability data support the claimed shelf life of 36 months. No special storage conditions are required.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since ondansetron is 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

This product is generic formulation of Zofran Melt, which are available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ondansetron is a well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.
For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Dissolution tests have been performed in pH 1.2, pH 4.5 and pH 6.8. The composition of the different strengths is dose proportional.
The bioequivalence study was carried out with the highest strength of ondansetron.
The conclusions of the biostudy with the 8 mg orodispersible tablets can be extrapolated for the 4 mg strength of ondansetron.

Bioequivalence study

One Bioequivalence study was conducted to determine whether the test product, Ondansetron 8 mg ODT, and the reference product, Zofran® Melt 8 mg (manufactured by GlaxoSmithKline) are bioequivalent.

The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of products administered without water, in normal, healthy adult, human subjects under fasting conditions, with a screening period of 28 days prior to the first dose of IMP administration.

Analytical/statistical methods:
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV% [1]
$AUC_{(0-t)}$	93.8	87.43 - 100.68	14.3
$AUC_{(0-\infty)}$	93.5	86.87 - 100.73	15.0
C_{max}	95.9	89.54 - 102.75	13.9

Pharmacokinetic Parameter	Arithmetic Means (± SD)	
	Test Product-T	Reference Product-R
$AUC_{(0-t)}$	301.224 ± 130.9254	320.771 ± 134.4264
$AUC_{(0-\infty)}$	316.978 ± 144.5964	338.892 ± 149.7279
C_{max}	41.516 ± 14.8933	43.236 ± 15.0562
t_{max} [1]	2.000 (1.000 - 3.517)	2.000 (1.000 - 4.000)

Relative Bioavailability Results for Ondansetron (N = 24)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	38.992	40.651	95.9	89.54 - 102.75	13.9	100.0
$lnAUC_{0-t}$	275.097	293.214	93.8	87.43 - 100.68	14.3	99.9
$lnAUC_{0-\infty}$	287.468	307.312	93.5	86.87 - 100.73	15.0	99.9

Conclusion on bioequivalence study:
Based on the submitted bioequivalence study, it can be concluded that Ondansetron 8 mg orodispersible tablets (Test) and Zofran® Melt 8 mg oral lyophilized (Reference) are bioequivalent in terms of rate and extent of absorption of a single dose of one ondansetron orodispersible tablet 8 mg under fasting conditions administered without water.

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for this generic application.

IV.4 Clinical efficacy

To support the application, the applicant has submitted as report bioequivalence study. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

IV.5 Clinical safety

There were no adverse events during the conduct of the study. There were no clinically significant findings in the vital signs assessment, 12-lead ECG recording or the laboratory tests in any of the subjects in the study.

IV.6 Risk Management Plan

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 Ondansetron STADA 4 mg, 8 mg orodispersible tablets.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Zofran Melt. No new clinical studies were conducted. The MAH demonstrated through bioequivalence study that the pharmacokinetic profile of the Ondansetron 8 mg orodispersible tablets is similar to the pharmacokinetic profile of the Zofran® Melt 8 mg oral lyophilized reference product. Risk management is adequately addressed. The conclusions of the biostudy with the 8 mg orodispersible tablets can be extrapolated for the 4 mg strength.

This generic medicinal product can be used instead of the reference products.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ondansetron 4 mg, 8 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic form of Zofran Melt 8 mg oral lyophilisate. Zofran Melt are well-known medicinal products with established favourable efficacy and safety profiles.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The decentralised procedure was finalised with a positive outcome on 16 April, 2025.

Summary Public Assessment Report

Generics

Ondansetron STADA 4 mg, 8 mg orodispersible tablets
LT/H/0209/001-002/DC

Ondansetron STADA Arzneimittel AG 4 mg, 8 mg orodispersible tablets
LT/H/0228/001-002/DC

Ondansetron

Date: 18 June 2025

Summary Public Assessment Report

Generics

Ondansetron 4 mg, 8 mg orodispersible tablets
Active substance: Ondansetron

This is a summary of the public assessment report (PAR) for Ondansetron 4 mg, 8 mg orodispersible tablets. It explains how Ondansetron 4 mg, 8 mg orodispersible tablets were assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Ondansetron 4 mg, 8 mg orodispersible tablets.

For practical information about using Ondansetron 4 mg, 8 mg orodispersible tablets, patients should read the package leaflet or contact their doctor or pharmacist.

Ondansetron STADA and what is it used for?

Ondansetron 4 mg, 8 mg orodispersible tablets is a 'generic medicine'. This means that Ondansetron 4 mg, 8 mg orodispersible tablets is similar to a 'reference medicine' already authorised in the European Union (EU) called Zofran Melt 8 mg oral lyophilisate.
Ondansetron orodispersible tablets is used in the treatment:

Adults
For the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults.

Paediatric population
For the management of chemotherapy-induced nausea and vomiting in children aged ≥ 6 months.

How does Ondansetron STADA work?

Ondansetron tablets contains a medicine called ondansetron. This belongs to a group of medicines called serotonin antagonists.

How is Ondansetron STADA used?

The pharmaceutical form is orodispersible tablet and the route of administration is oral.

What benefits of Ondansetron STADA have been shown in studies?

Because Ondansetron STADA is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Zofran Melt. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Ondansetron STADA?

Because Ondansetron orodispersible tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

Why is Ondansetron STADA approved?

It was concluded that, in accordance with EU requirements, Ondansetron orodispersible tablets has been shown to have comparable quality and to be bioequivalent to Zofran Melt. Therefore, the State Medicines Control Agency of Lithuania decided that, as for reference medicine called Zofran Melt, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ondansetron STADA?

A risk management plan has been developed to ensure that Ondansetron orodispersible tablets is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Ondansetron orodispersible tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Ondansetron STADA

In Lithuania, the marketing authorisation for Ondansetron orodispersible tablets was granted on 19.05.2025.

The full PAR for Ondansetron orodispersible tablets can be found on the website https://mri.cts-mrp.eu/portal/home?domain=h. For more information about treatment with Ondansetron orodispersible tablets, read the package leaflet (*link*) or contact your doctor or pharmacist.

This summary was last updated in June 2025.

Viešojo vertinimo protokolo apžvalga
Ondansetron STADA 4 mg, 8 mg burnoje disperguojamos tabletės
Ondansetron STADA Arzneimittel AG 4 mg, 8 mg burnoje disperguojamos tabletės
Ondansetronas

Trumpa kokybinės dalies apžvalga

Vaistinio preparato veiklioji medžiaga – ondansetronas. Ondansetrono gamintojas pateikė veikliosios medžiagos gamybos bylą (ASMF).
Gatavo produkto gamintojo veikliosios medžiagos ondansetrono specifikacija yra tinkamos kokybės ir atitinka ES gairių reikalavimus. Pateikti serijų analizės sertifikatai atitinka patvirtintos specifikacijos reikalavimus.

Ondansetron 4 mg burnoje disperguojamos tabletės
Apvali, balta arba balkšva, plokščia tabletė nuožulniais kraštais, abipus lygiu paviršiumi, kurios skersmuo – 8 mm ± 0,3 mm.
Ondansetron 8 mg burnoje disperguojamos tabletės
Apvali, balta arba balkšva, plokščia tabletė nuožulniais kraštais, kurios vienos pusės paviršius lygus, o kitoje pusėje įspausta „8“, tabletės skersmuo – 11 mm ± 0,3 mm.

Gatavo produkto sudėtyje yra šių pagalbinių medžiagų: manitolio, koloidinio bevandenio silicio dioksido, bazinio butilinto metakrilato kopolimero, manitolio granulių, krospovidono, aspartamo, braškių kvapiosios medžiagos ir magnio stearato.. Pagalbinių medžiagų pasirinkimas yra pagrįstas, jos yra plačiai naudojamos farmacinių preparatų gamyboje.
Bioekvivalentiškumo tyrimai atlikti su referenciniu vaistiniu preparatu Zofran Melt 8 mg geriamasis liofilizatas. Gamybos metodas standartinis. Gatavo produkto išleidimo ir tinkamumo laiko pabaigos specifikacijų kokybė atitinka ES gairių reikalavimus. Analizės procedūrų aprašymai pateikti, metodai yra validuoti. Serijų analizės sertifikatai atitinka specifikacijos reikalavimus. Gatavas produktas pakuojamas į aliuminio-aliuminio lizdines plokšteles. Gatavo produkto stabilumo tyrimai atlikti pagal ES gairių reikalavimus. Remiantis stabilumo tyrimų duomenimis nustatytas 36 mėnesių tinkamumo laikas. Šiam vaistiniam preparatui specialių laikymo sąlygų nereikia.

Trumpa ikiklinikinės ir klinikinės dalies apžvalga

Ondansetron 4 mg, 8 mg burnoje disperguojamos tabletės yra receptinis vaistinis preparatas skirtas:

- ląstelėms toksinės (citotoksinės) chemoterapijos sukeltam pykinimui ir vėmimui slopinti vaikams (nuo 6 mėnesių iki 17 metų) ir suaugusiesiems;
- pooperacinio pykinimo ir vėmimo profilaktikai suaugusiesiems;
- spindulinio gydymo sukeltam pykinimui ir vėmimui slopinti suaugusiesiems.

Paraiška registruoti vaistinį preparatą pateikta pagal direktyvos 2001/83/EB 10 str. 1d. („generinis“). Pareiškėjas įrodė, kad vaistinis preparatas Ondansetron 4 mg, 8 mg burnoje disperguojamos tabletės yra iš esmės panašios į referencinį vaistinį preparatą Zofran® Melt 8 mg geriamąjį liofilizatą.

Ondansetronas yra stiprus, labai selektyvaus poveikio 5-HT3 receptorių antagonistas.
Tikslus mechanizmas, kuriuo ondansetronas kontroliuoja pykinimą ir vėmimą, nėra žinomas. Chemoterapiniai vaistiniai preparatai ir spindulinis gydymas gali skatinti 5-HT išsiskyrimą plonojoje žarnoje ir per 5-HT3 receptorius aktyvuodami nervo klajoklio aferentines skaidulas sukelti vėmimo refleksą. Ondansetronas blokuoja šio reflekso sukėlimą. Nervo klajoklio

aferentinių skaidulų aktyvavimas gali skatinti 5-HT išsiskyrimą area postrema, kuris yra ketvirtojo smegenų skilvelio dugne, ir sukelti vėmimą veikiant centriniams mechanizmams. Vadinasi, ondansetrono poveikis (citotoksinės chemoterapijos ir spindulinio gydymo sukelto pykinimo ir vėmimo kontrolė) tikriausiai pasireiškia dėl jo antagonizmo 5-HT3 receptoriams ir periferinės, ir centrinės nervų sistemos neuronuose. Ondansetrono veikimo mechanizmas pooperacinio pykinimo ir vėmimo atveju nežinomas, tačiau galimi tokie patys mechanizmai, kaip ir citotoksinių medžiagų sukelto pykinimo bei vėmimo atveju.Klinikiniais tyrimais nustatyta, kad YAZ silpnos antimineralkortikoidinės savybės pasireiškia silpnu antimineralkortikoidiniu poveikiu.

Ondansetrono farmakodinaminės, farmakokinetinės ir toksikologinės savybės yra gerai žinomos.
Kadangi pateikta generinė paraiška, yra referuojama į referencinio vaistinio preparato tyrimų duomenis, todėl naujų ikiklinikinių tyrimų duomenų pareiškėjas nepateikė.
Ondansetron 4 mg, 8 mg burnoje disperguojamos tabletės yra per burną vartojamas vaistinis preparatas, jo kiekybinė ir kokybinė sudėtis tokios pat kaip referencinio vaistinio preparato Zofran® Melt 8 mg geriamojo liofilizato. Pateiktas klinikinis tyrimas, įrodantis šių vaistinių preparatų biologinį ekvivalentiškumą. Referencinė ir pripažįstančios valstybės narės sutarė, kad Ondansetron veiksmingumo ir saugumo duomenys yra panašūs į Zofran Melt.

Remiantis pateiktais kokybės, saugumo ir veiksmingumo duomenimis, decentralizuotoje procedūroje dalyvaujančios referencinė valstybė narė (Lietuva) ir pripažįstančios valstybės narės (Belgija, Liuksemburgas, Vokietija, Danija, Suomija, Prancūzija, Ispanija, Norvegija, Švedija) nutarė, kad vaistinį preparatą Ondansetron STADA 4 mg, 8 mg burnoje disperguojamos tabletės/ Ondansetron STADA Arzneimittel AG 4 mg, 8 mg burnoje disperguojamos tabletės registruoti galima ir europinė fazė buvo sėkmingai baigta (210 dieną) 2025-04-16.
Lietuvoje vaistinis preparatas užregistruotas 2025-05-19.