Medicines & Healthcare products Regulatory Agency

MHRA

# Public Assessment Report

# National Procedure

# ONDANSETRON 4 MG ORODISPERSIBLE TABLETS
# ONDANSETRON 8 MG ORODISPERSIBLE TABLETS

## Ondansetron

## PL 12762/0649-50

## Mercury Pharmaceuticals Limited

# LAY SUMMARY

**Ondansetron 4 mg orodispersible tablets**
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**Ondansetron**

This is a summary of the Public Assessment Report (PAR) for Ondansetron 4 mg and 8 mg orodispersible tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Ondansetron 4 mg and 8 mg orodispersible tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

## What are Ondansetron 4 mg and 8 mg orodispersible tablets and what are they used for?

These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the United Kingdom (UK) called Zofran Melt 4 mg and Zofran Melt 8 mg.

Ondansetron 4 mg and 8 mg orodispersible tablets are used for:

- preventing nausea and vomiting caused by chemotherapy (in adults and children) or radiotherapy for cancer (adults only).
- preventing nausea and vomiting after surgery (adults only).

## How do Ondansetron 4 mg and 8 mg orodispersible tablets work?

These medicines contain the active ingredient ondansetron. This belongs to a group of medicines called antiemetics, which work by blocking the actions of chemicals in the body that can trigger nausea and vomiting.

Ondansetron 4 mg and 8 mg orodispersible tablets dissolve very quickly when put on top of the tongue.

## How are Ondansetron 4 mg and 8 mg orodispersible tablets used?

The pharmaceutical form of these medicines is an orodispersible tablet and the route of administration is oral (by mouth).

The dose prescribed will depend on the treatment the patient is having.

<u>To prevent nausea and vomiting from chemotherapy or radiotherapy</u>
On the day of chemotherapy or radiotherapy, the usual adult dose is 8 mg taken one or two hours before treatment and another 8 mg twelve hours after treatment.
On the following days, the usual adult dose is 8 mg twice a day. This may be given for up to 5 days.

In children aged over 6 months and adolescents, the doctor will decide the dose depending on the child's size (body surface area) or weight. Further information is included on the label.
The usual dose for a child is up to 4 mg twice a day and this can be given for up to 5 days.

<u>To prevent nausea and vomiting after an operation</u>
The usual adult dose is 16 mg before the operation.
For children aged over 1 month and adolescents, it is recommended that ondansetron is given

as an injection using a different medicinal product.

In patients with moderate or severe liver problems, the total daily dose should not be more than 8 mg. Ondansetron tablets should start to work within one or two hours of taking a dose.

If the patient is sick (vomits) within one hour of taking a dose, they should take the same dose again. Otherwise they should not take more Ondansetron tablets than the label says. If the patient continues to feel sick, they should tell their doctor or nurse.

For further information on how Ondansetron 4 mg and 8 mg orodispersible tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

**What benefits of Ondansetron 4 mg and 8 mg orodispersible tablets have been shown in studies?**
Because Ondansetron 4 mg and 8 mg orodispersible tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. 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 4 mg and 8 mg orodispersible tablets?**
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicines. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Because Ondansetron 4 mg and 8 mg orodispersible tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

**Why were Ondansetron 4 mg and 8 mg orodispersible tablets approved?**
It was concluded that, Ondansetron 4 mg and 8 mg orodispersible tablets have been shown to be comparable to and to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Ondansetron 4 mg and 8 mg orodispersible tablets?**
A Risk Management Plan (RMP) has been developed to ensure that Ondansetron 4 mg and 8 mg orodispersible tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, 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 and reviewed continuously.

**Other information about Ondansetron 4 mg and 8 mg orodispersible tablets**
Marketing Authorisations for Ondansetron 4 mg and 8 mg orodispersible tablets were granted in the UK on 03 November 2021.

The full PAR for Ondansetron 4 mg and 8 mg orodispersible tablets follows this summary.

This summary was last updated in December 2021.

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# I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Ondansetron 4 mg and 8 mg orodispersible tablets (PL 12762/0649-0650) could be approved.

The products are approved for the following indications:
Adults:

- For the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
- For the prevention of post-operative nausea and vomiting (PONV).
- For treatment of established PONV, administration by injection is recommended.

Paediatric Population:

- For the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months
- No studies have been conducted on the use of orally administered ondansetron in the prevention and treatment of PONV in children aged ≥1 month, administration by IV injection is recommended for this purpose.

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.

Ondansetron does not alter plasma prolactin concentrations.
The role of ondansetron in opiate-induced emesis is not yet established.

These applications were approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Zofran Melt 4 mg and Zofran Melt 8 mg, that has been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the UK on 03 November 2021.

# II QUALITY ASPECTS

## II.1 Introduction

These products consist of orodispersible tablets containing 4 mg or 8 mg of ondansetron.

In addition to ondansetron, these products also contain the excipients mannitol colloidal anhydrous silica, basic butylated methacrylate copolymer, granular mannitol, crospovidone Type A, aspartame, magnesium stearate and strawberry flavour.

The finished products are packaged in aluminium-aluminium blister packs in a pack size of 10 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

## II.2 ACTIVE SUBSTANCE

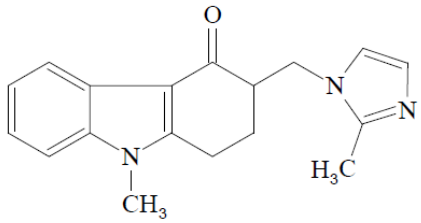
**rINN: Ondansetron**

Chemical Name: 4H-Carbazol-4-one,1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]

(±)-2,3-Dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carbazol-4(1H)-one

Molecular Formula: $C_{18}H_{19}N_3O$

Chemical Structure:




Molecular Weight: 293.36

Appearance: White to off-white powder

Solubility: Very soluble in hydrochloric acid and in formic acid

Ondanestron is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

## II.3 DRUG PRODUCTS

### Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the final products.

These products do not contain or consist of genetically modified organisms (GMO).

### Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

# III NON-CLINICAL ASPECTS

## III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

### III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

### III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

### III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

### III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

### III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

## IV CLINICAL ASPECTS

### IV.1 Introduction
The clinical pharmacology, efficacy and safety of ondanestron are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

### IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study.

This study was an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study comparing the test product Ondansetron 8 mg orodispersible tablets, versus the reference product Zofran Melt 8 mg, in subjects under fasted conditions.

Subjects were administered a single oral dose (8 mg) of either the test or the reference product, after an overnight fasting of at least 10 hours. The subjects were instructed to let the tablet completely disintegrate in their mouth. The subjects were instructed to swallow the resulting suspension when the orodispersible tablet was completely disintegrated. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 8 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

**Descriptive statistics**

| Parameters (Units) | Mean ± SD (Un-transformed data) | |
|---|---|---|
| | Test Product-T | Reference Product-R |
| $T_{max}$ (h)[#] | 2.000 (1.000 - 3.517) | 2.000 (1.000 - 4.000) |
| $C_{max}$ (ng/mL) | 41.516 ± 14.8933 | 43.236 ± 15.0562 |
| $AUC_{0-t}$ (ng.h /mL) | 301.224 ± 130.9254 | 320.771 ± 134.4264 |
| $AUC_{0-\infty}$ (ng.h /mL) | 316.978 ± 144.5964 | 338.892 ± 149.7279 |
| $\lambda_z$ (1/h) | 0.143 ± 0.0203 | 0.134 ± 0.0257 |
| $t_{½}$ (h) | 4.968 ± 0.8012 | 5.346 ± 0.9802 |
| AUC_%Extrap_obs (%) | 4.276 ± 2.3201 | 4.561 ± 2.2739 |

[#]$T_{max}$ is represented as median (min-max) value.

**Relative bioavailability**

| 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 |

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 8 mg product strength can be extrapolated to the 4 mg strength.

## IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

## IV.4 Clinical efficacy

No new efficacy data were submitted with these applications and none were required.

## IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

### IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

### IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

## V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ondanestron is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


Ondansetron 4 mg orodispersible tablets
ondansetron
10 tablets
4 mg
MercuryPharma
Marketing Authorisation Holder:
Mercury Pharmaceuticals Limited
Capital House, 85 King William Street, London EC4N 7BL, UK
5 021691 002697
Ondansetron 4 mg orodispersible tablets
ondansetron
Each orodispersible tablet contains 4 mg of Ondansetron
Also contains Mannitol, Silica colloidal anhydrous, Basic butylated methacrylate copolymer, Mannitol granular, Crospovidone Type A, Aspartame, Magnesium stearate, Strawberry flavour
See leaflet for further information.
For oral administration only.
Place the tablet on the tongue and allow to disperse, then swallow.
Read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Use as directed by your physician.
PL 12762/0649
POM
Affix dispensing label here
varnish free area for Serialisation details.
EXP:
Batch :
PC:
SN:


MercuryPharma
Ondansetron 4 mg orodispersible tablets
FL-121058-01
PL 12762/0649


Ondansetron 8 mg orodispersible tablets
ondansetron
10 tablets
8 mg
MercuryPharma
Marketing Authorisation Holder:
Mercury Pharmaceuticals Limited
Capital House, 85 King William Street, London EC4N 7BL, UK
5 021691 002703
Ondansetron 8 mg orodispersible tablets
ondansetron
Each orodispersible tablet contains 8 mg of Ondansetron
Also contains Mannitol, Silica colloidal anhydrous, Basic butylated methacrylate copolymer, Mannitol granular,Crospovidone Type A, Aspartame, Magnesium stearate, Strawberry flavour
See leaflet for further information.
For oral administration only.
Place the tablet on the tongue and allow to disperse, then swallow.
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KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Use as directed by your physician.
PL 12762/0650
POM
Affix dispensing label here
varnish free area for Serialisation details.
EXP:
Batch :
PC:
SN:


MercuryPharma
Ondansetron 8 mg orodispersible tablets
FL-121059-01
PL 12762/0650

# TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

| **Application type** | **Scope** | **Product information affected** | **Date of grant** | **Outcome** | **Assessment report attached Y/N** |
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