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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ondansetron Aurobindo 4 mg and 8 mg, film-coated tablets Aurobindo Pharma B.V., the Netherlands

ondansetron hydrochloride dihydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2677/001-002/MR
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Pharmacotherapeutic group:	Serotonin (5HT3) antagonists
ATC code:	A04AA01
Route of administration:	oral
Therapeutic indication:	the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy in adults and children aged ≥ 6 months; prevention and treatment of post-operative nausea and vomiting in adults and children aged ≥ 1 month
Prescription status:	prescription only
Date of first authorisation in NL:	27 September 2010
Concerned Member States:	Mutual recognition procedure with DE, DK, FI, MT, SE and UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ondansetron Aurobindo 4 mg and 8 mg, film-coated tablets, from Aurobindo Pharma B.V. The date of authorisation was on 27 September 2010 in the Netherlands.

The product is indicated for:

- Adults: Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV).
- Paediatric population: Ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months, and for the prevention and treatment of PONV in children aged ≥ 1 month.

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

Ondansetron is a potent, highly selective 5-HT3 receptor-antagonist. Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT3 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.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Zofran 4 mg and 8 mg, film-coated tablets which have been registered in Belgium by GlaxoSmithKline Pharma A/S since 23 May 1990 (original product). In the Netherlands, Zofran Zydis 4 mg and 8 mg, orodispersible tablets (NL License RVG 21471-21472) have been registered since 6 July 1998. The authorisation for Zofran film-coated tablets has been withdrawn in the Netherlands. In addition, reference is made to Zofran authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Zofran 8 mg, film-coated tablets, registered in the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ondansetron hydrochloride dihydrate, an established active substance described in the European, British and US Pharmacopoeia (Ph.Eur., BP, USP*). The active substance is a white to almost white powder, which is soluble in methanol, sparingly soluble in water and alcohol, and slightly soluble in methylene chloride. Different polymorphic forms exist, the drug substance manufacturer is consistently producing the crystalline form. Ondansetron hydrochloride dihydrate has one optically active carbon and therefore it can exist as two different enantiomers. Both enantiomers are known to be pharmaceutically active and the ondansetron hydrochloride dihydrate manufactured is a racemic mixture.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The MAH refers to the specifications of the Ph.Eur. monograph for ondansetron hydrochloride dihydrate and the additional CEP requirements. The limits for two impurities are more stringent than required in the monograph. Additional requirements of the MAH regard microbiological quality, particle size and bulk density. The specification is acceptable in view of the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been assessed by the EDQM.

** Ph.Eur., BP and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, UK or USA respectively.*

Medicinal Product

Composition
Ondansetron Aurobindo 4 mg are white to off-white, oval shaped, film-coated tablets debossed with ‘E’ on one side and ‘01’ on the other side.
Ondansetron Aurobindo 8 mg are yellow, oval shaped, film-coated tablets debossed with ‘E’ on one side and ‘02’ on the other side.

The film-coated tablets are packed in PVC/aluminium blisters.

The excipients are:

Tablet core: lactose anhydrous, cellulose microcrystalline (E460), starch pregelatinised (maize), magnesium stearate (E572).
Film-coating 4 mg: hypromellose (E464), triacetin (E1518), titanium dioxide (E171).
Film-coating 8 mg: hypromellose (E464), triacetin (E1518), titanium dioxide (E171), iron oxide yellow (E172).

The excipients and packaging are usual for this type of dosage form. The core tablets are dose weight proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to formulate a drug comparable to the innovator product (Zofran) marketed by GlaxoSmithKline. Comparative dissolution profiles were provided, showing similarity between the innovator product and the reference products. The choices of the packaging and manufacturing process are justified. The test and reference products used in the bioequivalence studies are acceptable from chemical point of view.

Manufacturing process
The tablets are manufactured by means of an 18 step process. After sieving the active substance and excipients, the product is mixed into a common blend. The blend is lubricated, compressed and coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scaled batches for both strengths, which is acceptable in view of the Note for Guidance on Process Validation. The product is manufactured using conventional manufacturing techniques and is considered to be a standard process. An acceptable protocol for the validation of additional production batches has been provided.

Control of excipients
The excipients comply with the specifications of the Ph.Eur., except for Opadry coating. The in-house specification of the Opadry coating is acceptable; the components of the Opadry coating comply with the Ph.Eur, NF (National Formulary) or JPE (Japanese Pharmaceutical Excipients). Additional tests are proposed for cellulose microcrystalline, magnesium stearate, triacetin and hypromellose. Purified water is not only controlled as per Ph.Eur., it also complies with the USP. All specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification active (HPLC and TCL), and colorants, average weight, dissolution, content uniformity, assay, related substances, thickness, water content and microbiological quality. The release and end of shelf-life specifications are identical, except for dissolution and thickness. The limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical results on three production scaled batches of both strengths were provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three production scaled batches of each strength stored at 25°C/60% RH (36/9 monhts) and 40°C/75% RH (6 months). The batches were stored in PVC/Aluminium blisters. For the bulk pack stored at 25°C/60% RH data is available for 12 months. The conditions used in the stability studies are according to the ICH stability guideline. No specific changes or patterns were noted. A photostability study was performed. The product is not sensitive to light. The granted storage time and conditions are 36 months with no special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, except for lactose monohydrate. The milk used in the manufacturing of lactose monohydrate is sourced from healthy animals and collected under the same conditions as milk for human consumption. For the other excipients, the theoretical risk of transmitting TSE can be excluded.

Several post-approval commitments have been made with regard to the finished product; these can be found on page 8 of this report.

II.2 Non-clinical aspects

This product is a generic formulation of Zofran 4 mg and 8 mg, film-coated tablets, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ondansetron released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ondansetron Aurobindo 8 mg, film-coated tablets (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Zofran 8 mg, film-coated tablets (GlaxoSmithKline, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open-label, randomised, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioequivalence study was carried out under fasted conditions in 30 (+ 2 stand-by) healthy adult male subjects, aged 18 - 41 years with a mean age of 26 years. Each subject received a single dose (8 mg) of one of the 2 ondansetron formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected at prior to dosing and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours after administration of the products.

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.

Results
One subject was withdrawn from the study prior to the second dosing period because of a non drug-related event (malaria). He was replaced with one of the two stand-by subjects and therefore the analysis was conducted with 30 subjects who completed the study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ondansetron under fasted conditions.

Treatment N=30	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	243 ± 111	254 ± 114	37.7 ± 12.7	1.89
Reference	266 ± 102	280 ± 107	39.2 ± 11.2	2.00
***Ratio (90% CI)**	0.91 (0.86-0.95)	0.90 (0.86-0.95)	0.95 (0.89-1.02)	-
CV (%)	11	11	15	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ondansetron under fasted conditions, it can be concluded that Ondansetron Aurobindo 8 mg, film-coated tablets and the Zofran 8 mg, film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Ondansetron may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ondansetron. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Biowaiver

A biowaiver for the 4 mg strength is accepted with the following justification:

- Ondansetron 4 mg and 8 mg tablets are manufactured by the same manufacturer using the same manufacturing process.
- Pharmacokinetics is linear across the relevant 4 mg and 8 mg ondansetron dose range. The highest dose 8 mg dose was chosen for the bioequivalence study.
- The qualitative composition of ondansetron 4 mg tablets is the same as that of ondansetron 8 mg tablets.
- Ondansetron 4 mg tablets are dose proportional with ondansetron 8 mg tablets. Thus, the ratio of amount of active substance and the excipients is the same for both the strengths.
- The dissolution profiles of the 4 mg and 8 mg tablets were found to be similar in different media i.e. water, 0.1N HCl, pH-4.5 Acetate buffer and pH-6.8 Phosphate buffer.

Risk management plan

Ondansetron was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ondansetron can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their

disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for other ondansetron containing products.

Readability test
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 test consisted two rounds with 10 participants each, including a pilot round. The 23 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each question met the criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ondansetron Aurobindo 4 mg and 8 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zofran 4 mg and 8 mg, film-coated tablets. Zofran is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other ondansetron containing products.

The Board followed the advice of the assessors. Ondansetron Aurobindo 4 mg and 8 mg, film-coated tablets were authorised in the Netherlands on 27 September 2010.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ondansetron Aurobindo 4 mg and 8 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 24 August 2012.

The date for the first renewal will be: 23 August 2017.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH commits to perform process validation on the first three consecutive batches for ondansetron tablets. The results for the process validation studies shall be held available at the manufacturing location for the inspectorate.
- The MAH commits to continue long-term stability studies (at 25°C ± 2°C and 60% ± 5% RH) on the first production batch for each strength of ondansetron 4 mg & 8 mg film-coated tablets.
- The MAH commits to perform accelerated stability studies (at 40°C ± 2°C and 75% ± 5% RH) and long-term stability studies (at 25°C ± 2°C and 60% ± 5% RH) on the first three commercial batches of maximum batch size for each strength of ondansetron 4 mg & 8 mg tablets.
- The MAH commits to perform long-term stability studies on a minimum of one production batch per year in the marketed pack.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH: CSP implementation (SI/H/PSUR/001/002; Nov. 2012)	NL/H/2677/ 001-002/IB/ 001	IB	8-4-2013	3-7-2013	Approval	N
Introduce of the PSMF to replace the Detailed Description of Pharmacovigilance System in accordance with new pharmacovigilance legislation in all the member states.	NL/H/2677/ 001-002/IA/ 002/G	IA/G	26-6-2013	26-7-2013	Approval	N
Submission of an updated Ph.Eur. certificate of suitability for Ondansetron hydrochloride dihydrate drug substance from an already approved manufacturer.	NL/H/2677/ 001-002/IA/ 003	IA	4-7-2013	3-8-2013	Approval	N