Safeguarding public health

MHRA

Public Assessment Report

Ondansetron 4mg Film-coated Tablets

PL 20223/0003

Ondansetron 8mg Film-coated Tablets

PL 20223/0004

Medicines and Healthcare products Regulatory Agency

ONDANSETRON 4MG TABLETS
PL 20223/0003

ONDANSETRON 8MG TABLETS
PL 20223/0004

UKPAR

TABLE OF CONTENTS

ONDANSETRON 4MG TABLETS
PL 20223/0003

ONDANSETRON 8MG TABLETS
PL 20223/0004

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted M. R. Pharma GmbH Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg and 8mg Film-coated Tablets (PLs 20223/0003-4). These are prescription only medicines [POMs] used to prevent or treat feelings of sickness (nausea) and actual sickness (vomiting) caused by chemotherapy, radiotherapy or surgery.

These products contain the active substance ondansetron hydrochloride dihydrate. It is thought that chemotherapy and radiotherapy release a hormone known as serotonin (5HT) in the gut. The serotonin then acts by means of pathways known as $5HT_3$ receptors to cause nausea and vomiting. Ondansetron may block serotonin from acting on these $5HT_3$ receptors. It is likely that ondansetron acts in a similar way to prevent or treat nausea and vomiting following surgery.

The clinical data presented to the MHRA, before licensing, demonstrated that Ondansetron 4mg and 8mg Film-coated Tablets are essentially similar or equivalent to the approved products, Zofran 4mg and 8mg Tablets, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Ondansetron 4mg and 8mg Film-coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.

ONDANSETRON 4MG FILM-COATED TABLETS
PL 20223/0003

ONDANSETRON 8MG FILM-COATED TABLETS
PL 20223/0004

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Ondansetron 4mg and 8mg Film-coated Tablets (PLs 20223/0003-4) to M. R. Pharma GmbH on 4 May 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Zofran Tablets from Belgium, which were authorised in February 1990.

These products contain the active ingredient ondansetron hydrochloride dihydrate and are 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.

Ondansetron is a potent, highly selective $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

PHARMACEUTICAL ASSESSMENT

LICENCE NO:	**PLs 20223/0003-0004**
PRODUCT NAME:	**Ondansetron 4mg & 8mg Film-coated Tablets**
ACTIVE(S):	**Ondansetron hydrochloride dihydrate**
COMPANY NAME:	**M. R. Pharma GmbH**
E.C. ARTICLE:	**10.1(a)(iii) of Directive 2001/83/EC**
LEGAL STATUS:	**POM**

INTRODUCTION

These national standard abridged applications are for film-coated tablets containing 4mg & 8mg of the serotonin ($5HT_3$) antagonist ondansetron (as hydrochloride dihydrate). The products are 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.

These applications were submitted under the first paragraph of Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to the original products authorised in February 1990 in Belgium under the brand name Zofran. The products authorised in the UK are Zofran 4mg and 8mg Tablets currently authorised to Glaxo Wellcome UK Limited as PL 10949/0110-0111 following a change of ownership in December 1993. These products were originally authorised in March 1990 to Glaxo Operations UK Limited. The reference products have therefore been authorised in the EU for more than 10 years.

No paediatric development plan exists for these products.

These proposed products have not been authorised to the applicant or to a related company in any other European Union (EU) member state, nor are they the subject of any pending application in any other EU member state.

SUMMARIES

Introduction and Quality Overall Summary (QOS)

A satisfactory Introduction and Quality Overall Summary have been provided.

DRUG SUBSTANCE

General information

Nomenclature

rINN: Ondansetron hydrochloride
Ph.Eur. name: Ondansetron hydrochloride dihydrate
USP name: Ondansetron hydrochloride

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

(±)-4-H-carbazol-4-one, 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-monohydrochloride dihydrate

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

Structure

$C_{18}H_{19}N_30$. HCl. $2H_2O$ MW: 365.86

General properties

Ondansetron hydrochloride dihydrate is a white to off-white crystalline powder sparingly soluble in water and alcohol, soluble in methanol, slightly soluble in dichloromethane, very slightly soluble in acetone, chloroform and in ethyl acetate.

Solubility in water is 3.2% and 0.8% in 0.9% saline. The pH of an aqueous 1% w/v solution is approximately 4.6. The pKa is 7.4 such that free base precipitates when the pH is above the range 5.7-7.

Ondansetron hydrochloride dihydrate is more stable in acidic media than at neutral pH.

Ondansetron contains a single asymmetric carbon and is used as the racemate. There are no literature reports of polymorphism.

Manufacture

Manufacturer

A suitable site for manufacturing the drug substance has been named.

Manufacturing process description and process controls

A letter of access to the drug master file (DMF) and the open/applicant's part of the DMF, (presented in Common Technical Document [CTD] format) have been provided for the named manufacturing site. The applicant's part is identical to the version held by the MHRA. This source of drug substance has previously been accepted for applications authorised in the UK; the applications therefore attract a standard abridged fee.

In converting from the old EU-format to CTD format, the European Drug Master File (EDMF) holder has proposed changes to the drug substance specification to reflect the current Ph.Eur. monograph for ondansetron hydrochloride dihydrate. The EDMF file states that the manufacturing process, manufacturing site, and solvents and reagents used are unchanged. The specification has been updated in line with the Ph.Eur. monograph, updated stability data have been provided and specifications for some of the reagents and starting materials have been revised. The EDMF is considered suitable.

The synthetic route has been described.

Control of materials

A signed declaration has been provided confirming that no materials of animal origin are used in manufacture of the drug substance.

Control of drug substance

Specification

Ondansetron hydrochloride dihydrate is the subject of a Ph.Eur. monograph. The substance is also described in the USP/NF. Batches of drug substance are controlled by the drug substance manufacturer and finished product manufacturer to a suitable specification.

Analytical procedures / Validation of analytical procedures

Most of the tests performed by the drug substance manufacturer and manufacturer of the finished product use the methods described in the Ph.Eur. monograph. In-house methods are used.

Suitable validation and verification studies have been performed on the analytical methods to confirm their suitability for use.

Justification of specification

The applicant has provided a justification for the proposed specification that was based on the Ph.Eur. monograph for ondansetron hydrochloride.

Reference standards or materials

Satisfactory reference standards are described. Certificates of Analysis are provided as appropriate.

Container closure system

The drug substance is packed in a suitable container.

Stability

Satisfactory stability studies have been presented.

DRUG PRODUCT

Description and composition of the drug product

Table 1: Composition of ingredients.

Ingredient	Reference Standard
Core:	
Ondansetron hydrochloride dihydrate (equivalent to ondansetron)	Ph.Eur.
Lactose (monohydrate)	Ph.Eur.
Microcrystalline cellulose	Ph.Eur.
Maize starch	Ph.Eur.
Magnesium stearate	Ph.Eur.
Purified water	Ph.Eur.
Film-coating:	
Opadry yellow Y-1-7000 White containing:	HSE
Hydroxypropylmethylcellulose 2910	
Titanium dioxide E171	
Macrogol/PEG 400	
Purified water	Ph.Eur.

Pharmaceutical development

Components of the drug product

Excipients were selected with consideration to those included in the reference products, but with a different coating formulation. The function of each ingredient has been described. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies. Results of excipient-active compatibility studies have been reported, showing no evidence of incompatibility. The tablets are film-coated to protect the drug substance that is sensitive to light.

Formulation development

A satisfactory summary of the development of the product has been provided, including details of scale-up.

Comparative *in vitro* dissolution profiles have been generated for the biobatches of the test product Ondansetron 8mg Tablets and the UK reference product Zofran 8mg Film-coated Tablets and for the 4mg tablets from both manufacturers. Testing was performed as for routine batch release. Both test and reference products studied in the bioequivalence study showed similar release profiles.

Physicochemical and biological properties

A satisfactory summary of the physicochemical properties of the drug substance has been provided.

Manufacturing process development

A satisfactory summary of the development and scale-up studies leading to adoption of the manufacturing process has been provided.

Container and closure system

Conventional PVC/PVdC/Al blisters have been selected. This pack is suitable.

Manufacture

Manufacturer(s)

The named manufacturing site has been inspected by the UK Inspectorate. The site was considered suitable for manufacture of solid dosage forms. A copy of the UK close out letter has been provided.

Batch release and assembly sites are also identified.

Batch formula

Satisfactory formulae have been provided for the manufacture of batches of 4mg and 8mg tablets.

Description of manufacturing process and process controls

A flow chart of the manufacturing process has been provided.

The in-process controls and acceptance criteria are acceptable.

Process validation and/or evaluation

The process has been validated by the finished product manufacturer.

All in-process results comply with the proposed acceptance criteria demonstrating the consistency of the manufacturing process. The process may be considered validated.

Control of excipients

Specifications

All excipients included in the tablet cores and purified water used in preparation of the coating suspension are tested for compliance with the current relevant Ph.Eur. monographs. A satisfactory specification and test methods have been provided for the commercial coating formulation.

Satisfactory Certificates of Analysis have been provided for all ingredients used in the manufacture of the products.

Excipients of human or animal origin

It is stated in the application forms that lactose (as monohydrate) is of animal origin but it is not considered susceptible to TSE. A declaration has also been provided that magnesium stearate is manufactured from stearic acid of plant origin.

A declaration has been provided for lactose monohydrate that milk from goats and sheep is not used.

Confirmation has also been provided that lactose monohydrate used in the tablets is derived from the milk of healthy cows, in the same condition as milk collected for human consumption. It is further confirmed that no other materials of animal origin, apart from the calf rennet, are used in the preparation of lactose monohydrate.

No genetically modified organisms are included in these products.

Control of drug product

Specification

Suitable finished product specifications have been provided.

Analytical procedures / Validation of analytical procedures

Analytical procedures are described and validated as appropriate.

Batch analysis

Satisfactory Certificates of Analysis have been provided for batches of 4mg and 8mg tablets manufactured.

Justification of specifications

A justification for the release and shelf-life specifications has been provided.

Reference standards or materials

The primary reference standard for ondansetron hydrochloride dihydrate has been described.

A satisfactory Certificate of Analysis has been provided.

Satisfactory Certificates of Analysis for reference standards of known impurities have been provided.

Container closure system

The tablets are presented in transparent PVC/PVdC/aluminium blisters. The tablets will be presented in packs containing 2, 4, 6, 9, 10, 15, 30, 50, 100 and 500 tablets.

Satisfactory supplier and finished product manufacturer specifications and Certificates of Analysis have been provided for examples of the packaging components. The specification for PVC/PVdC film includes an identification test (IR). The materials are suitable for food use and comply with Directive 90/128/EEC (as amended).

Stability

Stability data have been provided for three batches of 4mg and 8mg tablets. All batches were stored in PVC/PVdC/Al blisters as proposed for marketing.

The analytical methods were as described for routine batch release.

Stability data provided: 25°C/60% (18 months), and 40°C/75% (6 months).

The results of a stability study into the effect of light have been presented. No requirements for storage recommendations follow from this study.

Only minor changes attributable to analytical variation were seen in samples stored under the above conditions.

The applicant has proposed a shelf-life of 3 years for product not carrying any storage directions. This is acceptable on the basis of the data provided.

BIOEQUIVALENCE/BIOAVAILABILITY

Ondansetron is rapidly absorbed from the gastrointestinal tract and reaches maximum concentration in serum after approximately 1.6 hours. It is reported that there is some increase in bioavailability in the presence of food, although this is not thought to be clinically significant. There is a literature report (Clin. Pharmacokinet. 29 [2] 1995) of a non-proportional increase in systemic availability with 8mg, 16mg, 32mg and 64mg of ondansetron that may be the result of saturation of the first-pass metabolism.

Comparative *in vitro* dissolution profiles have been generated for the biobatches of test product Ondansetron 8mg Tablets and the UK reference product Zofran 8mg Film-coated Tablets, and for 4mg tablets from both manufacturers. Testing was performed as for routine batch release. Both test and reference products studied in the bioequivalence study showed similar release profiles.

Study number:	Protocol No. SACT 21/2004 (September 2004)
Test product:	Ondansetron 8mg Film-coated Tablets (as proposed for marketing).
Reference product:	Zofran Tablets 8 mg (Glaxo Wellcome UK).
Number of patients:	26 healthy male volunteers were enrolled and completed the study.

The results of this study are presented in the Clinical Assessment report. A satisfactory Certificate of Analysis has been provided for the test product.

The applicant has provided a justification for not performing a study with the 4mg tablets. A biowaiver is accepted given that linear kinetics apply between 4mg and 8mg, proportional formulae for the tablet cores have been used and similar dissolution results have been shown for the two strengths. The criteria for biowaiver are satisfied.

Plasma concentrations of ondansetron were determined using a validated HPLC method. A satisfactory validation report has been provided.

MARKETING AUTHORISATION APPLICATION FORMS

Satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), LABELLING & PATIENT INFORMATION LEAFLET

Satisfactory.

STATEMENT ABOUT THE AUTHOR OF THE QUALITY OVERALL SUMMARY

A suitable Pharmaceutical Expert is named and the report is satisfactory.

CONCLUSIONS

Marketing authorisations may be granted.

The requirements of essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the drug substance. Bioequivalence of the test and reference products has been shown at a single dose of 8mg. In addition, similar dissolution results and impurity profiles have been demonstrated for the proposed and reference products.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE NO:	**PLs 20223/0003-4**
PRODUCT NAME:	**Ondansetron 4mg and 8mg Film-coated Tablets**
ACTIVE(S):	**Ondansetron hydrochloride dihydrate**
COMPANY NAME:	**M. R. Pharma GmbH**
E.C. ARTICLE:	**{Generic Application} Article 10.1 (a) (iii)**
LEGAL STATUS:	**POM**
ATC CODE:	**A04A A01**

INTRODUCTION AND BACKGROUND

Ondansetron is a potent highly selective $5HT_3$ receptor antagonist 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.

These are two generic abridged applications for film-coated tablets containing 4mg and 8 mg ondansetron.

The two applications are submitted under the provisions of Directive 2001/83/EC Article 10.1(a)(iii), claiming that the products are essentially similar to the proprietary product Zofran 4mg Tablets, authorised in Belgium on 23 February 1990. In the UK, Zofran 4mg and 8mg Tablets were initially granted licences on 7 March 1990 (as PLs 00004/0376-7) but are now licensed to Glaxo Wellcome UK as PLs 10949/0110-1. This is considered satisfactory.

The applications have been made in CTD format. This is satisfactory.

The application contains a study report of a randomised, 2-way crossover, bioequivalence study undertaken to characterise the relative bio-availability from one 8mg tablet of the reference product, UK Glaxo Wellcome Zofran tablets, with M. R. Pharma's proposed 8mg tablets. This is satisfactory.

INDICATIONS

The indication is:

Ondansetron film-coated tablets are 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.

This is satisfactory and fully consistent with the SmPC for Zofran 4mg & 8mg tablets, PLs 10949/0110-1.

DOSE & DOSE SCHEDULE

The proposed dose and dosage schedules for these products are considered satisfactory.

TOXICOLOGY

Not assessed.

CLINICAL PHARMACOLOGY

Pharmacokinetics

A comparative bioavailability study comparing the test product, Ondansetron 8mg Tablets with Zofran 8mg Tablets (Glaxo Wellcome, UK) has been submitted.

The study has been designed according to current scientific standards and the respective CPMP guidelines ("Note for Guidance on Good Clinical Practice" [CPMP/ICH/135/95] and "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" [CPMP/EWP/QWP/1401/98]).

This was a single dose crossover study in 26 healthy male volunteers. The results of the bioequivalence study with the 8mg strength are also valid for the 4mg tablets since, according to the above mentioned guidance (CPMP/EWP/QWP/1401/98), the conduct of only one bioequivalence study with the highest strength is acceptable for products with several strengths when all of the following conditions are met:

- pharmacokinetics have been shown to be linear over the therapeutic dose range;
- the qualitative composition of the different strengths is the same;
- the ratio between the active substance and the excipients is the same;
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Following an overnight fast, 26 healthy male volunteers received a single oral dose of 8 mg of ondansetron on two separate occasions with a washout period of at least seven days. In each phase, a total of 16 blood samples were taken at the following times: before drug administration (not more than 60 minutes pre-dose) as well as 15, 30, 45, 60, 90 minutes and 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12 and 24 hours post-dose.

Plasma samples were analysed using a specific and sensitive, validated method.

Primary efficacy parameters were C_{max} and AUC_{0-t}, secondary parameters $AUC_{0-\infty}$, $t_{1/2}$, MRT, and t_{max} ANOVA, two one-sided tests for bioequivalence and ratio analysis for untransformed and In-transformed primary pharmacokinetic parameters were performed. The results of this study are summarised below.

Table 1: Pharmacokinetic parameters after a single oral administration of 8mg ondansetron to 26 healthy volunteers (mean ± SD)

Primary parameters summary statistics					
Test parameter	**Summary statistics**	**Test product**	**Reference product**	**Conventional 90%CI***	**Point Estimate***
AUC_{0-t} (h.ng/ml)	Geometric mean	147	163	79.39% to 102.66%	90.28%
C_{max} (ng/ml)	Geometric mean	28	31	79.37% to 104.31%	90.99%

*Based on ln transformed data

AUC = area under the plasma concentration curve; C_{max} = maximum plasma concentration; CI = confidence interval

The statistical evaluation of all volunteers (Table 1) based on ln-transformed data resulted in point estimates of 90.3% (90% confidence interval: 79.4-102.6%) for AUC_{0-t} and 91% (90% confidence interval: 79.4-104.3%) for $C_{max.}$ The 90% CIs are slightly below the defined bioequivalence criteria indicating a small but significant difference between the drug formulations.

Inspection of the individual subject data revealed that in one subject the ratio of, eg, AUC_{0-t} was only 16.8%, while for all other subjects the ratio was between 57% and 123%. This pattern can be considered as an outlier allowing the exclusion of the subject of the statistical analysis (according to the Note for Guidance on Statistical Principles for Clinical Trials, CPMP/ICH/363/96).

The statistical analysis was therefore repeated after exclusion of the subject in question (Table 2), resulting in point estimates of 96.4% (90% confidence interval: 90.1-103.0) for AUC_{0-t} and 96.3% (90% confidence interval: 87.2-106.5%) for C_{max}. The 90% Cl are entirely included in the generally accepted bioequivalence range of 80-125% leading to the conclusion of bioeqiuvalence.

Table 2: Pharmacokinetic parameters after a single oral administration of 8 mg ondansetron to 25 healthy volunteers

Primary parameters summary statistics					
Test parameter	**Summary statistics**	**Test product**	**Reference product**	**Conventional 90%CI***	**Point Estimate***
AUC_{0-t} (h.ng/ml)	Geometric mean	159	165	90.12% to 103.02%	96.36%
C_{max} (ng/ml)	Geometric mean	30	31	87.17% to 106.45%	96.33%

*Based on ln transformed data

There were no clinically significant abnormalities in laboratory data in any of the subjects. Due to the exclusion of the subject of the evaluation, the intra-subject variability for AUC_{0-t} was halved from 27.6% to 13.8% and for C_{max} reduced from 29.4% to 20.8%.

The investigational products were well-tolerated. No serious adverse events were reported.

As the bioequivalence analysis including all 26 subjects only marginally exceeded the lower 90% Cl of 80%, and the exclusion of one subject resulted in a pronounced reduction of the variability, the exclusion is deemed justified. The establishment of bioequivalence between Ondansetron 8mg Tablets and Zofran 8mg Tablets can be considered acceptable.

Conclusion

The study design, analytical methodology and statistical evaluation of the presented bioequivalence trial are in accordance with the recommendations of the relevant CPMP guidelines. Therefore, the bioequivalence of the generic product with the referenced innovator product, marketed in UK by GlaxoSmithKline has been proven.

EFFICACY

No original data on the formulation proposed for marketing submitted for assessment.

SAFETY

No original data on the formulation proposed for marketing submitted for assessment.

EXPERT REPORT

A Clinical Overview and Clinical Summary has been provided.

Information about the Clinical Expert is provided.

This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET & LABELLING

Satisfactory.

CONCLUSIONS

There is no clinical objection to the grant of marketing authorisations. No new or unexpected safety concerns arise from these applications.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 4mg and 8mg Tablets 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 applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Ondansetron 8mg Film-coated Tablets and Zofran 8mg Tablets (PL 10949/0111).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Zofran 4mg and 8mg Tablets.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with ondansetron is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

ONDANSETRON 4MG FILM-COATED TABLETS
PL 20223/0003

ONDANSETRON 8MG FILM-COATED TABLETS
PL 20223/0004

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Ondansetron 4mg and 8mg Tablets on 28 March 2003.
2	The MHRA's assessment of the submitted data was completed on 4 July 2003.
3	Further information was requested from the company on 8 July 2003.
4	The applicant's response to further information (quality) request was received on 16 September 2003.
5	Further information (quality) was requested from the company on 12 December 2003.
6	The applicant's response to further information request (quality) was received on 21 January 2004.
7	Replacement data (clinical) was requested from the company on 9 July 2004.
8	Replacement data (clinical) was submitted by the company with letters dated 7 July 2005 and 15 December 2005.
9	The MHRA completed its assessment of the applications on 4 May 2006.
10	The applications were determined on 4 May 2006.

ONDANSETRON 4MG FILM-COATED TABLETS
PL 20223/0003

ONDANSETRON 8MG FILM-COATED TABLETS
PL 20223/0004

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4mg Ondansetron (as Ondansetron hydrochloride)

For excipients see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White coloured, circular, biconvex film-coated tablets debossed with '4' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ondansetron film-coated tablets are 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.

4.2. Posology and method of administration

Chemotherapy and radiotherapy induced nausea and vomiting

Adults:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Ondansetron film-coated tablets should be flexible in the range of 8-32 mg a day and selected as shown below.

Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For oral administration: 8mg 1-2 hours before treatment, followed by 8mg 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.

The recommended dose for oral administration is 8mg twice daily.

Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, Ondansetron can be given either by rectal, intravenous or intramuscular administration.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.

The recommended dose for oral administration is 8mg twice daily.

Children:

Ondansetron may be administered as a single intravenous dose of 5mg/m^2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily should be continued for up to 5 days after a course of treatment.

Elderly:

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Patients with Renal Impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic Impairment:

Clearance of Ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Post operative nausea and vomiting:

Adults:

For the prevention of PONV: Ondansetron can be administered orally or by intravenous or intramuscular injection.

For oral administration: 16mg one hour prior to anaesthesia. Alternatively, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

For the treatment of established PONV: Intravenous or intramuscular administration is recommended.

Children (aged 2 years and over):

For the prevention and treatment of PONV: Slow intravenous injection is recommended.

Elderly:

There is limited experience in the use of Ondansetron film-coated tablets in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron film-coated tablets are well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

Clearance of Ondansetron is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism:

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

4.3. Contraindications

Hypersensitivity to any component of the preparation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4. Special warnings and special precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

4.5. Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

4.6. Pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron film-coated tablets should not breastfeed their babies.

4.7. Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8. Undesirable effects

Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. The following side effects can occur: headache, a sensation of flushing or warmth, hiccups and occasional asymptomatic increases in liver function tests. There have been rare reports of immediate hypersensitivity reactions sometimes severe including anaphylaxis. Rare cases of transient visual disturbances (e.g: blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron. There have been rare reports suggestive of extrapyramidal reactions such as oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects. Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

4.9. Overdose

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with

transient second degree AV block. In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Ondansetron is a potent, highly selective $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ 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.

5.2. Pharmacokinetic properties

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 8mg dose. For doses above 8mg 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. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

The disposition of ondansetron following oral, intramuscular(IM) and intravenous(IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

Ondansetron is not highly protein bound (70-76%). 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.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

5.3. Preclinical safety data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Magnesium stearate
Hypromellose
Macrogol
Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions for storage

6.5. Nature and contents of container

PVC/PVdC blister with aluminium foil

Packages of 2, 4, 6, 9, 10, 15, 30, 50, 100 tablets
Hospital packs of 100 and 500 tablets

Not all pack sizes may be marketed.

6.6. Instruction for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

M.R. Pharma GmbH
Waldstrasse 30
D-22889 Tangestedt
Germany

8. MARKETING AUTHORISATION NUMBER

PL 20223/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/05/2006

10 DATE OF REVISION OF THE TEXT

04/05/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 8 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8mg Ondansetron (as Ondansetron hydrochloride)

For excipients see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White coloured, circular, biconvex film-coated tablets debossed with '8' on one side and central breakline on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ondansetron film-coated tablets are 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.

4.2. Posology and method of administration

Chemotherapy and radiotherapy induced nausea and vomiting

Adults:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Ondansetron film-coated tablets should be flexible in the range of 8-32 mg a day and selected as shown below.

Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For oral administration: 8mg 1-2 hours before treatment, followed by 8mg 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of

treatment.

The recommended dose for oral administration is 8mg twice daily.

Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, Ondansetron can be given either by rectal, intravenous or intramuscular administration.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.

The recommended dose for oral administration is 8mg twice daily.

Children:

Ondansetron may be administered as a single intravenous dose of 5mg/m^2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily should be continued for up to 5 days after a course of treatment.

Elderly:

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Patients with Renal Impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic Impairment:

Clearance of Ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Post operative nausea and vomiting:

Adults:

For the prevention of PONV: Ondansetron can be administered orally or by intravenous or intramuscular injection.

For oral administration: 16mg one hour prior to anaesthesia. Alternatively, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

For the treatment of established PONV: Intravenous or intramuscular administration is recommended.

Children (aged 2 years and over):

For the prevention and treatment of PONV: Slow intravenous injection is recommended.

Elderly:

There is limited experience in the use of Ondansetron film-coated tablets in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron film-coated tablets are well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

Clearance of Ondansetron is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism:

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

4.3. Contraindications

Hypersensitivity to any component of the preparation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4. Special warnings and special precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

4.5. Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

4.6. Pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron film-coated tablets should not breastfeed their babies.

4.7. Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8. Undesirable effects

Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. The following side effects can occur: headache, a sensation of flushing or warmth, hiccups and occasional asymptomatic increases in liver function tests. There have been rare reports of immediate hypersensitivity reactions sometimes severe including anaphylaxis. Rare cases of transient visual disturbances (e.g: blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron. There have been rare reports suggestive of extrapyramidal reactions such as oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects. Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

4.9. Overdose

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with

transient second degree AV block. In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Ondansetron is a potent, highly selective $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ 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.

5.2. Pharmacokinetic properties

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 8mg dose. For doses above 8mg 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. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

The disposition of ondansetron following oral, intramuscular(IM) and intravenous(IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

Ondansetron is not highly protein bound (70-76%). 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.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

5.3. Preclinical safety data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Magnesium stearate
Hypromellose
Macrogol
Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

No special precautions for storage

6.5. Nature and contents of container

PVC/PVdC blister with aluminium foil

Packages of 2, 4, 6, 9, 10, 15, 30, 50, 100 tablets
Hospital packs of 100 and 500 tablets

Not all pack sizes may be marketed.

6.6. Instruction for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

M.R. Pharma GmbH
Waldstrasse 30
D-22889 Tangestedt
Germany

8. MARKETING AUTHORISATION NUMBER

PL 20223/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/05/2006

10 DATE OF REVISION OF THE TEXT

04/05/2006

Patient Information Leaflet

ONDANSETRON 4MG FILM-COATED TABLETS
PL 20223/0003

ONDANSETRON 8MG FILM-COATED TABLETS
PL 20223/0004

Patient Information Leaflet

Ondansetron 4 mg film-coated tablets
Ondansetron 8 mg film-coated tablets
Ondansetron hydrochloride dihydrate

What you should know about Ondansetron film-coated tablets.
Please read this carefully before starting to take your medicine.

What your tablets contain
Each white coloured, circular, biconvex film-coated, tablet contains:
The active ingredient-ondansetron 4mg or 8mg (as ondansetron hydrochloride dihydrate) Other ingredients-lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate, hypromellose, macrogol, titanium dioxide.
Packs contain 30 x 4mg tablets or 10 x 8mg tablets.

Product Licence holder and manufacturer
Product Licence held by M.R. Pharma GmbH, Waldstrasse 30, D-22889 Tangstedt, Germany.
Manufactured by Specifar S.A, 11 Venizelou str., 123 51 Aigaleo, Athens, Greece or Millmount Healthcare Ltd., Units 5 - 7, Navan Enterprise Centre, Trim Road, Navan, Co. Meath., Ireland

What your tablets do
Ondansetron film-coated tablets contain ondansetron which belongs to a group of medicines called anti-emetics. Some medical and surgical treatments can make you feel sick or be sick (nausea and vomiting). Ondansetron film-coated tablets may stop these effects. If you are not sure why they have been prescribed for you, ask your doctor.

Before taking your tablets
- Have you been told you are allergic to ondansetron, any of the other ingredients in Ondansetron film-coated tablets listed above, or any similar medicines?
- Have you been told that you have a blockage in your gut or do you suffer from severe constipation?
- Do you think you may be pregnant?
- Are you breast-feeding?
- Have you been told your liver is not working as well as it should do?
- If the answer to any of these questions is yes: Did you tell your doctor at the last visit or an earlier visit?
  If you did NOT tell your doctor then you should do so as soon as possible and BEFORE starting the medicine. Your doctor will advise you about taking the medicine.

Important information about some of the ingredients of Ondansetron film-coated tablets:

This product contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Breast-feeding
The ondansetron in Ondansetron film-coated tablets may pass into the mother's milk. It is better therefore that mothers taking Ondansetron film-coated tablets do NOT breast-feed.

How to take your tablets
Look at the label- It should say WHO should take them, HOW MANY and WHEN. If it doesn't or you aren't sure, ask your doctor or pharmacist.
Ondansetron film-coated tablets can be prescribed for two reasons:
- to prevent feelings of sickness (nausea) and sickness (vomiting), or
- to treat nausea and vomiting

Swallow each tablet whole with a little water.

For patients receiving chemotherapy and/or radiotherapy that causes nausea and vomiting: the recommended dose is 8mg 1 or 2 hours before chemotherapy followed by 8mg 12 hours later. After the first 24 hours following chemotherapy, Ondansetron film-coated tablets can be given to prevent nausea and vomiting. The usual adult dose is 8mg twice a day, which can be given for up to 5 days.
If prescribed for a CHILD, make sure the tablets are taken as the label says. The usual dose for a child is up to 4mg twice a day, which can be given for up to 5 days, following chemotherapy.

To prevent nausea and vomiting after an operation: the usual adult dose is 16mg before the operation, or 8mg before the operation followed by two further doses of 8mg at eight hourly intervals.
For children aged 2 years and over it is recommended that ondansetron is given as an intravenous injection.

Patients with moderate or severe liver disease: the total daily dose should not be ore than 8mg.

What to do if you miss a dose
If you miss a dose and feel sick or vomit, take a tablet as soon as possible and then carry on as before. If you miss a dose but do not feel sick take the next dose as on the label.

What to do if you take too many tablets
It is important to stick to the dose on the label. Taking more than this could make you ill. If an overdose is taken, don't delay; ask your doctor what to do or contact your nearest hospital casualty department.

After starting to take your tablets
Ondansetron film-coated tablets should start to work within one or two hours of taking a dose. If you vomit a dose back within one hour then take the same dose again- otherwise do not take more tablets or take them more often than the label says. If you continue to feel sick then tell your doctor.

Most people find taking these tablets causes no problems. As with most medicines, a few people may find they have side effects.

Side effects
Along with its needed effects, a medicine may cause unwanted effects. Most people taking this medicine find it causes no problems. A few people can be allergic to some medicines; if any of the following rare side effects come on soon after taking these tablets, do not take any more tablets and tell your doctor IMMEDIATELY:

Sudden chest tightness or wheeziness
Swelling of eyelids, face or lips
Skin rash-red spots or hives (skin lumps)
Collapse

Other possible side effects are:
Headache
Feeling of warmth in the head or stomach
Hiccups
Light-headed feeling
Flushes of the face
Upset bowels-constipation

The following side effects are very rare but if you have them you should let your doctor know immediately:
Upward rolling of the eyes
Abnormal muscular stiffness, body movements or shaking
Fits
If you have any blood tests to check how your liver is working, this medicine may affect the results.
If you feel unwell or have any other unusual discomfort you don't understand, it is important to tell your doctor as soon as possible.

If you don't feel better
If your sickliness does not get better while taking Ondansetron film-coated tablets then tell your doctor.

Where to keep your tablets
Keep Ondansetron film-coated tablets safely away from children. A child may be harmed by medicine prescribed for someone else.

This medicinal product does not require any special storage conditions.

What to do with any unused tablets
If your doctor stops your treatment, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist. Do not use the tablets after the expiry date on the tablet foil or carton.

Remember
This medicine is for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if they have the same symptoms as you.

Further information
This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist who has the information you need and will advise you. You may well be able to find out more about prescribed medicines from books in public libraries.

YOU MAY WANT TO READ THIS LEAFLET AGAIN. PLEASE DO NOT THROW IT AWAY UNTIL YOU HAVE FINISHED YOUR MEDICINE.

The information provided applies only to Ondansetron film-coated tablets.

Leaflet updated December 2003

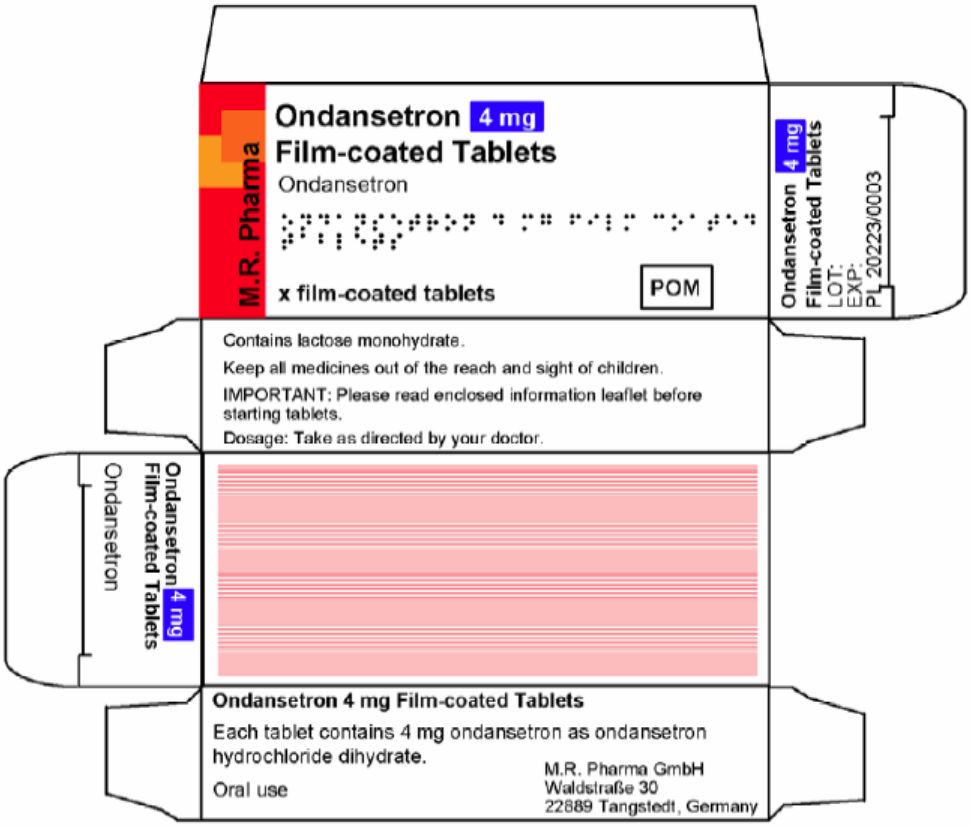
M.R. PHARMA GmbH

Labels/Packaging

ONDANSETRON 4MG FILM-COATED TABLETS

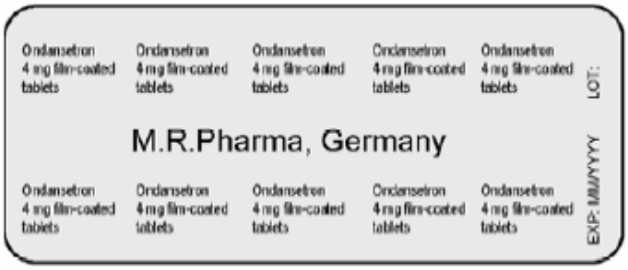
PL 20223/0003

1. Mock-up of the Outer Packaging



X = 2, 4, 6, 9, 10, 15, 30, 50, 100 tablets

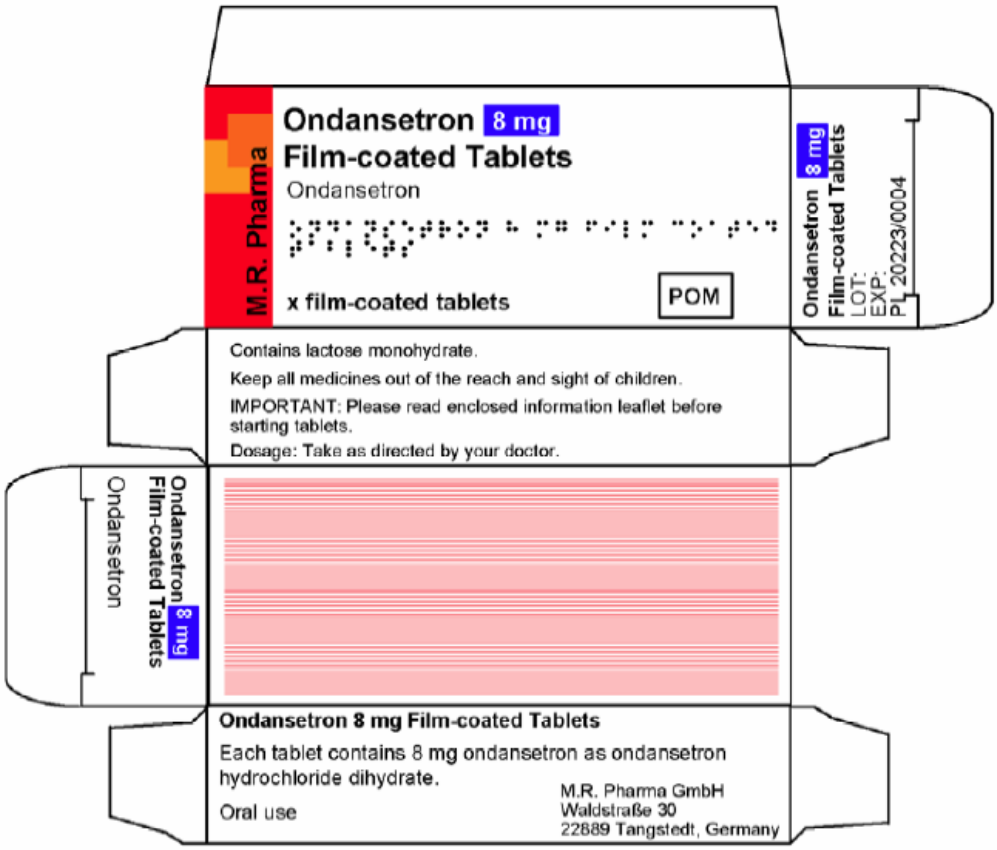
2. Mock-up of the Blister



ONDANSETRON 8MG FILM-COATED TABLETS

PL 20223/0004

1. Mock-up of the Outer Packaging



X = 2, 4, 6, 9, 10, 15, 30, 50, 100 tablets

2. Mock-up of the Blister