Safeguarding public health

MHRA

Public Assessment Report

Ondansetron 4mg/2ml Solution for Injection

PL 20223/0009

Ondansetron 8mg/4ml Solution for Injection

PL 20223/0010

Medicines and Healthcare products Regulatory Agency

ONDANSETRON 4MG/2ML SOLUTION FOR INJECTION
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PL 20223/0010

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ONDANSETRON 4MG/2ML SOLUTION FOR INJECTION
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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/2ml and 8mg/4ml Solution for Injection (PLs 20223/0009-10). 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/2ml and 8mg/4ml Solution for Injection are essentially similar or equivalent to the approved product, Zofran Injection 2mg/ml, 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/2ml and 8mg/4ml Solution for Injection outweigh the risks, hence Marketing Authorisations have been granted.

ONDANSETRON 4MG/2ML SOLUTION FOR INJECTION
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Ondansetron 4mg/2ml and 8mg/4ml Solution for Injection (PLs 20223/0009-10) 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 i.v. 4mg and 8mg from Germany, which were authorised in October 1990. The reference product authorised in the UK is Zofran Injection 2mg/ml (PL 00004/0375).

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

PL NUMBER: **PLs 20223/0009-0010**
PRODUCT: **Ondansetron 4mg/2ml & 8mg/4ml Solution for Injection**
ACTIVE: **Ondansetron hydrochloride dihydrate**
COMPANY: **M.R. Pharma GmbH**
E.C. ARTICLE: **10.1(a)(iii) of Directive 2001/83/EC**
LEGAL STATUS: **POM**

INTRODUCTION

These national complex and standard abridged applications are for an isotonic solution for injection containing 2mg/ml (4mg/2ml and 8mg/4ml) of the serotonin ($5HT_3$) antagonist ondansetron (as hydrochloride dihydrate). The applicant has proposed that 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 (PONV). The product may be administered by IM and IV injection.

The applications have been made under the first paragraph of Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Zofran i.v. 4mg and 8mg authorised to GlaxoSmithkline GmbH & Co. KG in Germany in October 1990. The reference product authorised in the UK is Zofran Injection 2mg/ml (PL 00004/0375). This product was authorised to Glaxo Operations UK Ltd trading as GlaxoSmithkline UK on 7 March 1990.

No paediatric development plan exists for this product.

The 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

$C_{18}H_{19}N_{3}0.\ HCl.\ 2H_2O$ 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 a 1% w/v solution in water is about 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 manufacturing site is named.

Manufacturing process description and process controls

A letter of access and the open (applicant's) part of the Drug Master File (DMF) have been provided for the source of active ingredient. The content is consistent with the most recent version of the applicant's part held on file at the MHRA. No products had been authorised in the UK using this source of active substance.

Control of materials

No materials of animal or human 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.

Analytical procedures / Validation of analytical procedures

The active substance manufacturer generally uses the methods described in the Ph.Eur. monograph. The methods are satisfactory.

The manufacturer of the finished product uses the methods described in the Ph.Eur. monograph.

Batch analyses

Satisfactory Certificates of Analysis have been provided.

Justification of specification

The applicant has provided a justification for the proposed specification.

Reference standards or materials

Satisfactory Certificates of Analysis have been provided for the current working standard of ondansetron hydrochloride dihydrate and for a reference standard. The reference standards are provided by the active substance manufacturer.

Container closure system

The drug substance is packed in a suitable container. The bags are stated as complying with Ph.Eur. requirements. Satisfactory specifications and batch documentation have been provided for the packaging components.

Stability

Satisfactory stability studies have been presented.

DRUG PRODUCT

Description and composition of the drug product

Table 1: Composition

Ingredient	Reference Standard
Ondansetron hydrochloride dihydrate (equivalent to ondansetron)	Ph.Eur
Citric acid monohydrate	Ph.Eur
Sodium citrate	Ph.Eur
Sodium chloride	Ph.Eur
Water for injections	Ph.Eur

Pharmaceutical development

Components of the drug product

Composition of the proposed product is based on the reference product. A satisfactory summary of product development has been provided.

No results of active substance - excipient compatibility studies have been conducted. Given that the ingredients are those used in the reference product and that long-term stability has been demonstrated, this is not considered to be a major deficiency. The applicant has referred to literature references on the sensitivity of ondansetron to light, and for the need to protect the product.

Brief discussion on reasons for inclusion of the ingredients has been provided. The levels are typical for a product of this nature.

Formulation development

A satisfactory summary of the development of the product has been provided.

With respect to impurity profile and qualitative and quantitative content the requirements of essential similarity are considered to have been achieved.

Compatibility with infusion fluids has been studied on the basis of the recommendations for the originator product. The results confirm the stability of the product when stored at 2-8°C and 25°C in 0.9% sodium chloride, 5% glucose, Ringer's Solution, 10% mannitol, 0.3% potassium chloride/0.9% sodium chloride and in 0.3% potassium chloride/5% glucose.

Physicochemical and biological properties

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

No reports of polymorphism have appeared in the literature.

Manufacturing process development

A summary of the development and scale-up studies have been provided.

Container and closure system

2ml and 5ml clear Type I glass ampoules are used. The products are packed in clear glass as is the originator product. This pack is suitable.

Manufacture

Manufacturer(s)

A suitable manufacturing site is named.

A copy of the current GMP Certificate for this site has been provided.

Batch formula

Satisfactory formulae have been provided for the manufacture of the 4mg/2ml and 8mg/4ml ampoules.

Description of manufacturing process and process controls

A copy of a flow chart of the manufacturing process has been provided.

Control of critical steps and intermediates

Satisfactory controls are described.

Process validation and / or evaluation

A copy of the process validation protocol has been provided. The protocol defines critical process parameters.

Control of excipients

Specifications

All ingredients comply with Ph.Eur. monographs. Specifications and supplier/finished product manufacturer Certificates of Analysis have been provided for sodium chloride, citric acid monohydrate, sodium citrate and water for injections.

Excipients of human or animal origin

It is stated on the marketing authorisation application forms that no materials of animal origin are contained in or used in the manufacture of this product.

No genetically modified organisms are included in these products.

Control of drug product

Specification

Satisfactory finished product specifications are provided.

Analytical procedures / Validation of analytical procedures

Analytical methods are described and validated as appropriate.

Batch analysis

Satisfactory Certificates of Analysis have been provided.

Characterisation of impurities

Information on all potential impurities has been provided.

Justification of specifications

Satisfactory justification has been provided.

Reference standards or materials

Satisfactory information on reference standards has been provided with Certificates of Analysis.

Container closure system

The product is presented in 2ml and 5ml capacity colourless Type I glass ampoules with green (4mg/2ml) and blue (8mg/4ml) One-Point-Cut (OPC) containing 2ml and 4ml solution, respectively. Ampoules are supplied in packs of 1, 2, 5, 6, 10, 25, 50 and 5 x 50 ampoules.

The ampoules are provided as open-funnel ampoules.

Supplier's drawings, finished product manufacturer specifications and Certificates of Analysis have been provided for consignments of 2ml and 5ml ampoules.

Stability

Stability data have been provided for batches manufactured in the proposed commercial ampoules.

Analytical methods used were as described for routine batch release.

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

Only minor changes attributable to analytical variation were seen.

The applicant has proposed a shelf-life of 12 months for product labelled with "Do not store above 30°C". According to the conclusions of the stability study, due to the known sensitivity of ondansetron to light, the product should be protected from light. It is therefore appropriate for the product to be labelled with "Keep container in the outer carton". An in-use shelf-life of 24 hours (after dilution) has been proposed for product stored at 2-8°C. This is consistent with the originator product and considered acceptable.

BIOEQUIVALENCE/BIOAVAILABILITY

Bioequivalence studies are not necessary to support this application.

MARKETING AUTHORISATION APPLICATION FORMS

Satisfactory.

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

Satisfactory.

STATEMENT ABOUT THE AUTHOR OF THE OVERALL QUALITY SUMMARY

A satisfactory *curriculum vitae* has been provided for the Pharmaceutical Expert.

CONCLUSIONS

Marketing authorisations may be granted.

The requirements of essential similarity are met with respect to qualitative and quantitative content of the drug substance. Given the route of administration, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

PL NUMBER:	**PLs 20223/0009-0010**
PRODUCT:	**Ondansetron 4mg/2ml & 8mg/4ml Solution for Injection**
ACTIVE:	**Ondansetron hydrochloride dihydrate**
COMPANY:	**M.R. Pharma GmbH**
E.C. ARTICLE:	**10.1(a)(iii) of Directive 2001/83/EC**
LEGAL STATUS:	**POM**

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 national abridged marketing authorisation applications.

The application was submitted under the provisions of Article 10.1(a)(iii) of Directive 2001/83/EC claiming that the product is essentially similar to Zofran i.v. 4mg and 8mg authorised to GlaxoSmithkline GmbH & Co. KG in Germany in October 1990. The reference product authorised in the UK is Zofran Injection 2mg/ml (PL 00004/0375). This product was authorised to Glaxo Operations UK Ltd trading as GlaxoSmithkline UK on 7 March 1990.

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the proprietary product Zofran injection. This is considered acceptable. See below.

These applications have been made in Common Technical Document format.

INDICATIONS

The proposed indication is consistent with the SmPC for Zofran 2 mg/ml injection, PL 00004/0375. This is satisfactory.

DOSE & DOSAGE SCHEDULE

The proposed dose and dosage schedules for these products have been compared with the Summary of Product Characteristics approved for Zofran 2mg/ml injection, PL 00004/0375. This is satisfactory.

TOXICOLOGY

Not assessed.

CLINICAL PHARMACOLOGY

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

A Clinical Overview has been submitted. This states that the formulation of the proposed product is identical to the Glaxo Operations UK formulation.

Based on published CPMP guidelines on this topic, the similarity of formulations and the proposed route of administration are considered adequate justification for not undertaking a bioequivalence study. This is satisfactory.

EFFICACY

No original clinical trial data on the formulation proposed for marketing submitted for assessment. This is acceptable.

SAFETY

No original clinical safety data on the formulation proposed for marketing submitted for assessment. This is considered acceptable. No new or unexpected safety concerns are considered to arise from this MAA.

EXPERT REPORT

A Clinical Overview has been provided.

Information about the Clinical Expert has also been provided.

This is acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS, PATIENT INFORMATION LEAFLET & LABELLING

Satisfactory.

CONCLUSIONS

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

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 4mg/2ml and 8mg/4ml Solution for Injection 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

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essential similarity of the proposed product to the proprietary product Zofran Injection 2mg/ml (PL 00004/0375). This is acceptable as the formulations are similar and the same routes of administration are proposed.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Zofran Injection 2mg/ml.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. 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.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Ondansetron 4mg/2ml and 8mg/4ml Solution for Injection on 24 October 2003.
2	The MHRA's assessment of the submitted quality data was completed on 6 February 2004.
3	Further information (quality) was requested from the company on 24 February 2004.
4	The applicant's response to further information (quality) request was received on 8 July 2004.
5	The MHRA's assessment of the submitted clinical data was completed on 16 February 2005.
6	Further information (quality) was requested from the company on 25 February 2005.
7	The applicant's response to further information request (quality) was received on 23 May 2005.
8	Changes to the product particulars were requested from the company on 19 September 2005.
9	The applicant's response to the requested changes was received on 17 March 2006.
10	Additional changes were requested on 20 March 2006.
11	The applicant's response to additional changes was submitted on 22 March 2006.
12	The MHRA completed its assessment of the applications on 4 May 2006.
13	The applications were determined on 4 May 2006.

ONDANSETRON 4MG/2ML SOLUTION FOR INJECTION
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg/2 ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule containing 2 ml solution contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate). The strength of the solution is 2 mg/ml ondansetron.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
The aqueous solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ondansetron hydrochloride 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).

4.2. Posology and method of administration

<u>Chemotherapy and radiotherapy:</u>

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 hydrochloride should be flexible in the range of 8-32 mg a day and selected as shown below.

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

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron hydrochloride 8 mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

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

Highly emetogenic chemotherapy:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron hydrochloride can be given either by rectal, intravenous or intramuscular administration.
Ondansetron hydrochloride has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy
- A dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two or four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours
- A single dose of 32 mg diluted in 50-100 ml of saline or other compatible infusion fluid (*see Pharmaceutical Precautions*) and infused over not less than 15 minutes immediately before chemotherapy

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of ondansetron hydrochloride in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy.

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

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

Elderly:
Ondansetron hydrochloride 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, frequency of dosing or route of administration are required.

Patients with hepatic impairment:
Clearance of ondansetron hydrochloride 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 8 mg should not be exceeded.

Post-operative nausea and vomiting (PONV):

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

Ondansetron hydrochloride may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over):
For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For treatment of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There is limited data on the use of ondansetron hydrochloride in the prevention and treatment of PONV in children under 2 years of age.

Elderly:
There is limited experience in the use of ondansetron hydrochloride in the prevention and treatment of PONV in the elderly, however ondansetron hydrochloride is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment:
No alteration of daily dosage, frequency of dosing or route of administration are required.

Patients with hepatic impairment:
Clearance of ondansetron hydrochloride 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 8 mg 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.

4.4. Special warnings and 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium-free'.

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 co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepan, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Tramadol: Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

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 hydrochloride should not breast-feed 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 involuntary movement disorders such as extrapyramidal reactions e.g. 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.

Occasionally, hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

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

Pharmacotherapeutic group: Antiemetics and Antinauseants – Serotonin ($5HT_3$) antagonists, ATC code: A04A A01.

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.
The role of ondansetron in opiate-induced emesis is not yet established.

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 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. 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 140 litres. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.
A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

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 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100 ml/min at 3 years. Volume of distribution fell from about 75 litres at 12 years to 17 litres at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg 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 insignificantly, increase in elimination half-life (5.4 h). 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 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

Sodium chloride
Citric acid monohydrate
Sodium citrate
Water for injections

6.2. Incompatibilities

Ondansetron 4 mg/2 ml Solution for Injection should not be administered in the same syringe or infusion as any other medication.

6.3. Shelf life

12 months (unopened). 24 hours (dilutions stored at 2-8°C).

6.4. Special precautions for storage

Do not store above 30°C. Keep ampoules in the outer carton.

Dilutions of Ondansetron 4 mg/2 ml Solution for Injection in compatible intravenous infusion fluids are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place.

6.5. Nature and contents of container

Ondansetron 4 mg/2 ml Solution for Injection, is contained in 2 ml Type I colourless ampoules with a green marking for the One-Point-Cut.

There are packs of 1, 2, 5, 6, 10, 25, 50 and 5x 50 ampoules.

6.6. Instruction for use and handling

<u>Compatibility with intravenous fluids:</u>

Ondansetron 4 mg/2 ml Solution for Injection should only be admixed with those infusion solutions, which are recommended:

- Sodium chloride intravenous infusion 0.9 %
- Glucose intravenous infusion 5 %
- Mannitol intravenous infusion 10 %
- Ringer's intravenous infusion
- Potassium chloride 0.3 % and sodium chloride 0.9 % intravenous infusion
- Potassium chloride 0.3 % and glucose 5 % intravenous infusion

In keeping with good pharmaceutical practice, dilutions of Ondansetron 4 mg/2 ml Solution for Injection in intravenous fluids should be prepared at the time of infusion or stored at 2-8°C for no more than 24 hours before the start of administration.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type I glass bottles.

Dilutions of Ondansetron 4 mg/2 ml Solution for Injection in sodium chloride 0.9 % or in glucose 5 % have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron 4 mg/2 ml Solution for Injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs:

Ondansetron 4 mg/2 ml Solution for Injection may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the Ondansetron 4 mg/2 ml Solution for Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively):

Cisplatin:
Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil:
Concentrations up to 0.8 mg/ml (e.g. 2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-flourouracil infusions may contain up to 0.045% (w/v) magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre) administered over thirty minutes to one hour.

Ceftazidime:
Doses in the range 250 mg to 2000 mg, reconstituted with water for injections as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2 g ceftazidime), and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide:
Doses in the range 100 mg to 1 g, reconstituted with water for injections, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:
Doses in the range 10-100 mg reconstituted with water for injections, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone:
Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 32 mg of ondansetron diluted in 50-100 ml of a compatible infusion fluid over approximately 15

minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram – 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 1 mg/ml for ondansetron.

7. MARKETING AUTHORISATION HOLDER

M.R. Pharma GmbH
Waldstraße 30
22889 Tangstedt
Germany

8. MARKETING AUTHORISATION NUMBER

PL 20223/0009

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/4 ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule containing 4 ml solution contains 8 mg ondansetron (as ondansetron hydrochloride dihydrate). The strength of the solution is 2 mg/ml ondansetron.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
The aqueous solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ondansetron hydrochloride 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).

4.2. Posology and method of administration

<u>Chemotherapy and radiotherapy:</u>

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 hydrochloride should be flexible in the range of 8-32 mg a day and selected as shown below.

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

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron hydrochloride 8 mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

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

Highly emetogenic chemotherapy:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron hydrochloride can be given either by rectal, intravenous or intramuscular administration.
Ondansetron hydrochloride has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy
- A dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two or four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours
- A single dose of 32 mg diluted in 50-100 ml of saline or other compatible infusion fluid (*see Pharmaceutical Precautions*) and infused over not less than 15 minutes immediately before chemotherapy

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of ondansetron hydrochloride in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy.

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

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

Elderly:
Ondansetron hydrochloride 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, frequency of dosing or route of administration are required.

Patients with hepatic impairment:
Clearance of ondansetron hydrochloride 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 8 mg should not be exceeded.

Post-operative nausea and vomiting (PONV):

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

Ondansetron hydrochloride may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over):
For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg, either prior to, at or after induction of anaesthesia.

For treatment of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There is limited data on the use of ondansetron hydrochloride in the prevention and treatment of PONV in children under 2 years of age.

Elderly:
There is limited experience in the use of ondansetron hydrochloride in the prevention and treatment of PONV in the elderly, however ondansetron hydrochloride is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment:
No alteration of daily dosage, frequency of dosing or route of administration are required.

Patients with hepatic impairment:
Clearance of ondansetron hydrochloride 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 8 mg 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.

4.4. Special warnings and 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium-free'.

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 co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepan, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Tramadol: Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

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 hydrochloride should not breast-feed 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 involuntary movement disorders such as extrapyramidal reactions e.g. 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.

Occasionally, hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

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

Pharmacotherapeutic group: Antiemetics and Antinauseants – Serotonin ($5HT_3$) antagonists, ATC code: A04A A01.

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.
The role of ondansetron in opiate-induced emesis is not yet established.

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 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. 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 140 litres. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.
A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

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 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100 ml/min at 3 years. Volume of distribution fell from about 75 litres at 12 years to 17 litres at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg 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 insignificantly, increase in elimination half-life (5.4 h). 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 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

Sodium chloride
Citric acid monohydrate
Sodium citrate
Water for injections

6.2. Incompatibilities

Ondansetron 8 mg/4 ml Solution for Injection should not be administered in the same syringe or infusion as any other medication.

6.3. Shelf life

12 months (unopened). 24 hours (dilutions stored at 2-8°C).

6.4. Special precautions for storage

Do not store above 30°C. Keep ampoules in the outer carton.

Dilutions of Ondansetron 8 mg/4 ml Solution for Injection in compatible intravenous infusion fluids are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place.

6.5. Nature and contents of container

Ondansetron 8 mg/4 ml Solution for Injection, is contained in 5 ml Type I colourless ampoules with a blue marking for the One-Point-Cut.

There are packs of 1, 2, 5, 6, 10, 25, 50 and 5 x 50 ampoules.

6.6. Instruction for use and handling

Compatibility with intravenous fluids:

Ondansetron 8 mg/4 ml Solution for Injection should only be admixed with those infusion solutions, which are recommended:

- Sodium chloride intravenous infusion 0.9 %
- Glucose intravenous infusion 5 %
- Mannitol intravenous infusion 10 %
- Ringer's intravenous infusion
- Potassium chloride 0.3 % and sodium chloride 0.9 % intravenous infusion
- Potassium chloride 0.3 % and glucose 5 % intravenous infusion

In keeping with good pharmaceutical practice, dilutions of Ondansetron 8 mg/4 ml Solution for Injection in intravenous fluids should be prepared at the time of infusion or stored at 2-8°C for no more than 24 hours before the start of administration.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type I glass bottles. Dilutions of Ondansetron 8 mg/4 ml Solution for Injection in sodium chloride 0.9 % or in glucose 5 % have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron 8 mg/4 ml Solution for Injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs:

Ondansetron 8 mg/4 ml Solution for Injection may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the Ondansetron 8 mg/4 ml Solution for Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively):

Cisplatin:
Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil:
Concentrations up to 0.8 mg/ml (e.g. 2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-flourouracil infusions may contain up to 0.045% (w/v) magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre) administered over thirty minutes to one hour.

Ceftazidime:
Doses in the range 250 mg to 2000 mg, reconstituted with water for injections as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2 g ceftazidime), and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide:
Doses in the range 100 mg to 1 g, reconstituted with water for injections, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:
Doses in the range 10-100 mg reconstituted with water for injections, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone:

Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 32 mg of ondansetron diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram – 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 1 mg/ml for ondansetron.

7. MARKETING AUTHORISATION HOLDER

M.R. Pharma GmbH
Waldstraße 30
22889 Tangstedt
Germany

8. MARKETING AUTHORISATION NUMBER

PL 20223/0010

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/2ML SOLUTION FOR INJECTION
PL 20223/0009

ONDANSETRON 8MG/4ML SOLUTION FOR INJECTION
PL 20223/0010

M.R. Pharma

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Ondansetron Injection is and what it is used for
2. Before you take Ondansetron Injection
3. How to take Ondansetron Injection
4. Possible side effects
5. Storing Ondansetron Injection

Ondansetron
4 mg/2 ml and 8 mg/4 ml
Solution for Injection

The active substance is ondansetron (as hydrochloride dihydrate).
Other ingredients are sodium chloride, citric acid monohydrate, sodium citrate and water for injections.

Marketing Authorisation Holder
M.R. Pharma
Waldstraße 30
D-22889 Tangstedt
Germany

Manufacturer
Hikma Farmacêutica (Portugal), Lda.
Estrada do Rio da Mó n.º 8, 8A e 8B – Fervença
2705-906 Terrugem SNT
Portugal

1. What Ondansetron Injection is and what it is used for

Ondansetron Injection is a solution for injection, which is available as colourless glass ampoules containing 4 mg of ondansetron per 2 ml of solution and 8 mg of ondansetron per 4 ml of solution. Ondansetron Injection is packed in carton boxes of 5 ampoules.

The active substance of Ondansetron Injection belongs to a group of medicines known as antiemetics and antinauseants being used to prevent vomiting and nausea induced by some medical treatments.

2. Before you take Ondansetron Injection

Do not take Ondansetron Injection
- if you are allergic to ondansetron or any of the other ingredients

Take special care with Ondansetron Injection
- if you are allergic to other antiemetic medicines
- if you have intestinal obstruction
- if you suffer from severe constipation
- if you have any liver disease

Also tell your doctor if you are taking any of the following medicines:
- Phenytoin
- Carbamazepine
- Rifampicin
- Tramadol

Pregnancy
Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Your doctor will then decide whether you should receive Ondansetron Injection.

Breast-feeding
The ondansetron in Ondansetron Injection may pass into mother's milk. It is therefore better that mothers receiving Ondansetron Injection do not breast-feed.

Taking other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium-free'.

3. How to take Ondansetron Injection

Daily dosage is fixed according to your individual need. Your doctor will tell you how long your treatment with Ondansetron Injection will last.

Ondansetron Injection will usually be given by a doctor or nurse.

Ondansetron Injection can be prescribed for two reasons:
- to prevent feelings of sickness (nausea) and sickness (vomiting) or
- to treat nausea and vomiting

For patients receiving chemotherapy and/or radiotherapy that causes nausea and vomiting:
The recommended dose is 8 mg given by intravenous injection (into a vein) or
intramuscular injection (into a muscle), immediately before chemotherapy
followed by an 8 mg tablet after 12 hours.

For patients receiving chemotherapy that causes severe nausea and vomiting any of the following dose schedules are recommended:
- 8 mg given by intravenous or intramuscular injection, immediately before chemotherapy
- 8 mg given by intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg 2 to 4 hours apart, or by an intravenous infusion (drip) of 1 mg per hour for up to 24 hours.
- 32 mg given as an intravenous infusion (drip), over not less than 15 minutes, immediately before chemotherapy.

After the initial Ondansetron injection you may be given tablets or suppositories for up to 5 days to prevent any further nausea and vomiting.

If prescribed for a child, the dose depends on your child's weight and height, and is given by intravenous injection immediately before chemotherapy followed by a 4 mg tablet 12 hours later, which can be continued twice a day for up to 5 days following chemotherapy.

To prevent nausea and vomiting after an operation:
The usual adult dose is 4 mg given as an intravenous or intramuscular injection before the operation.
For children aged 2 years and over the dose is 0.1 mg per kilogram of body weight, up to a maximum of 4 mg, given as an intravenous injection before the operation.

To treat nausea and vomiting after an operation:
The usual adult dose is 4 mg given as an intravenous or intramuscular injection.
For children aged 2 years and over the dose is 0.1 m g per kilogram of body weight, up to a maximum of 4 mg, given as an intravenous injection.

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

If you have the impression that the effect of Ondansetron Injection is too strong or too weak, talk to your doctor.

Ondansetron Injection should start to work soon after having the injection. If you continue to be sick or feel sick, tell your doctor.

If you think you may have missed a dose or had too much, let your doctor or nurse know.

4. Possible side effects

Like all medicines, Ondansetron Injection can have side effects.
Ondansetron Injection is generally well tolerated. However, the following side effects may occur in some patients during treatment.

If any of the following rare side effects come on soon after having your injection, tell your doctor immediately:
- sudden chest tightness or wheeziness
- swelling of eyelids, face lips or tongue
- skin rash - red spots or hives (skin lumps)
- collapse
- upward rolling of the eyes
- abnormal muscular stiffness, body movements or shaking
- fits
- blurring of vision

If you experience any of these symptoms, advise your doctor as soon as possible:
- irregular or slow heartbeat
- dizziness or lightheaded feeling
- headache
- flushes of the face
- feeling of warmth in the head or stomach
- Irritation and redness at the site of injection
- upset bowels, constipation
- hiccups

If you have any blood tests to check how your liver is working, this medicine may affect the results.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing Ondansetron Injection

Keep out of the reach and sight of children.

Do not store above 30°C. Keep ampoules in the outer carton to protect from light.

Ondansetron Injection should not be used if the ampoule is damaged or contains particles or is cloudy.

Do not use after the expiry date stated on the carton box.

This leaflet was prepared in March 2006.

Technical Leaflet

1.3.3 TECHNICAL PACKAGE LEAFLET

NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg/2 ml and 8 mg/4 ml Solution for Injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule containing 2 ml solution contains 4 mg ondansetron and each ampoule containing 4 ml solution contains 8 mg ondansetron (as ondansetron hydrochloride dihydrate). The strength of the solution is 2 mg/ml ondansetron.

PHARMACEUTICAL FORM

Solution for injection
The aqueous solution is clear and colourless.

POSOLOGY AND METHOD OF ADMINISTRATION

Chemotherapy and radiotherapy:

Adults and elderly:

Emetogenic chemotherapy and radiotherapy:
Ondansetron hydrochloride 8 mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

Highly emetogenic chemotherapy:
The following dose schedules over the first 24 hours of chemotherapy are effective:

- A single dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy
- A dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two or four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours
- A single dose of 32 mg diluted in 50-100 ml of saline or other compatible infusion fluid (*see Pharmaceutical Precautions*) and infused over not less than 15 minutes immediately before chemotherapy

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

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

Patients with renal impairment:
No alteration of daily dosage, frequency of dosing or route of administration is required.

Patients with hepatic impairment:
A total daily dose of 8 mg should not be exceeded.

Post-operative nausea and vomiting (PONV):

Adults and elderly:

Ondansetron hydrochloride may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over):
Ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For treatment of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

Patients with renal impairment:
No alteration of daily dosage, frequency of dosing or route of administration is required.

Patients with hepatic impairment:
A total daily dose of 8 mg should not be exceeded.

Patients with poor sparteine / debrisoquine metabolism:
No alteration of daily dosage or frequency of dosing is required.

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium chloride
Citric acid monohydrate
Sodium citrate
Water for injections

Incompatibilities

Ondansetron Solution for Injection should not be administered in the same syringe or infusion as any other medication.

Shelf life

12 months (unopened). 24 hours (dilutions stored at 2-8°C).

Special precautions for storage

Do not store above 30°C. Keep ampoules in the outer carton.

Dilutions of Ondansetron Solution for Injection in compatible intravenous infusion fluids are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place.

Nature and contents of container

Ondansetron 4 mg/2 ml Solution for Injection, is contained in 2 ml Type I colourless ampoules with a green marking for the One-Point-Cut.
Ondansetron 8 mg/4 ml, Solution for Injection, is contained in 5 ml Type I colourless ampoules with a blue marking for the One-Point-Cut.

There are packs of 1, 2, 5, 6, 10, 25, 50 and 5x 50 ampoules.

Instructions for use and handling

Compatibility with intravenous fluids:

Ondansetron Solution for Injection should only be admixed with those infusion solutions, which are recommended:

- Sodium chloride intravenous infusion 0.9 %
- Glucose intravenous infusion 5 %
- Mannitol intravenous infusion 10 %
- Ringer's intravenous infusion
- Potassium chloride 0.3 % and sodium chloride 0.9 % intravenous infusion
- Potassium chloride 0.3 % and glucose 5 % intravenous infusion

Dilutions of Ondansetron Solution for Injection in intravenous fluids should be prepared at the time of infusion or stored at 2-8°C for no more than 24 hours before the start of administration.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type I glass bottles.
Dilutions of Ondansetron Solution for Injection in sodium chloride 0.9 % or in glucose 5 % have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron Solution for Injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs:

Ondansetron Solution for Injection may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the Ondansetron Solution for Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively):

Cisplatin:
Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil:
Concentrations up to 0.8 mg/ml (e.g. 2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-flourouracil infusions may contain up to 0.045% (w/v) magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre) administered over thirty minutes to one hour.

Ceftazidime:
Doses in the range 250 mg to 2000 mg, reconstituted with water for injections as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2 g ceftazidime), and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide:
Doses in the range 100 mg to 1 g, reconstituted with water for injections, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:
Doses in the range 10-100 mg reconstituted with water for injections, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone:
Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 32 mg of ondansetron diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram – 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 1 mg/ml for ondansetron.

MARKETING AUTHORISATION HOLDER

M.R. Pharma GmbH
Waldstraße 30
22889 Tangstedt
Germany

Manufacturer
HIKMA FARMACÊUTICA (PORTUGAL), LDA.
Estrada do Rio da Mó n.º 8, 8A e 8B – Fervença
2705-906 Terrugem SNT
Portugal

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

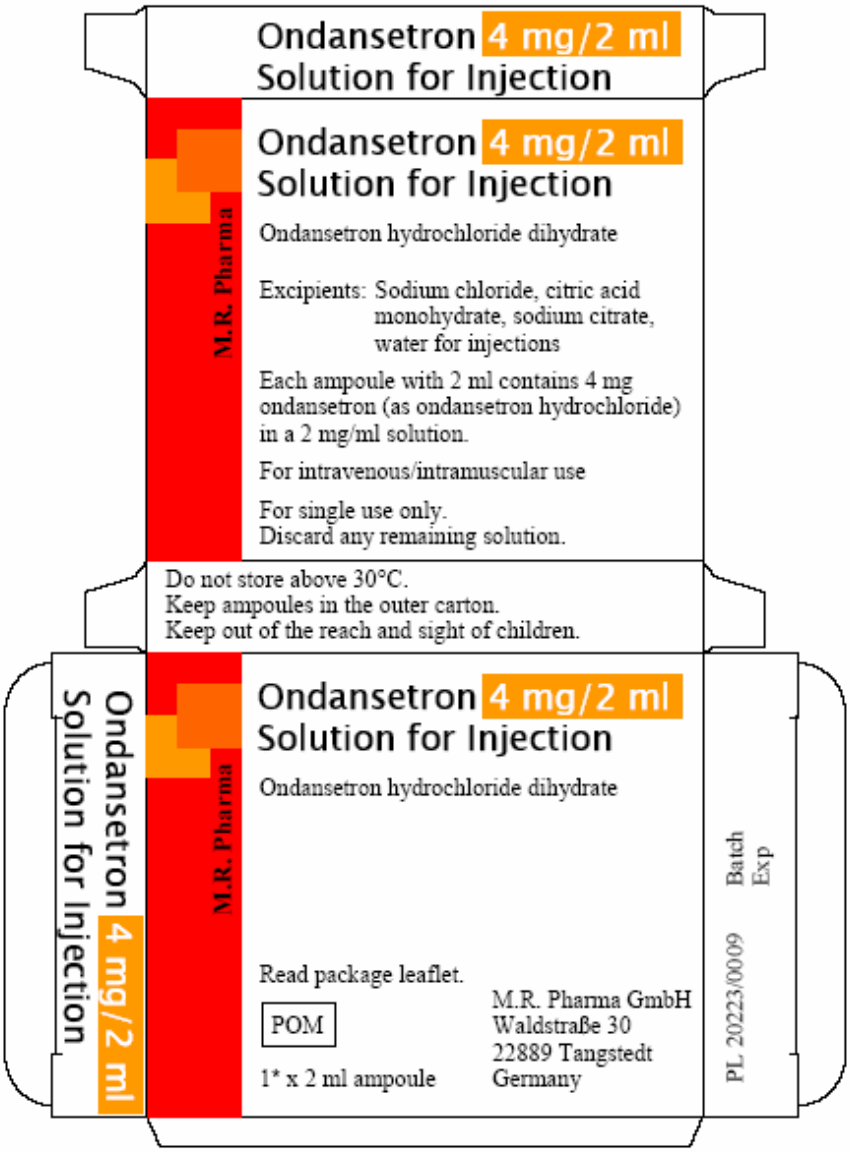
DATE OF REVISION OF THE TEXT

March 17, 2006

Labels/Packaging

ONDANSETRON 4MG/2ML SOLUTION FOR INJECTION
PL 20223/0009

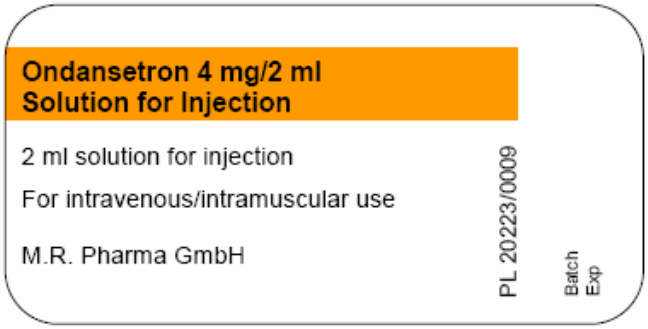
Outer box Ondansetron 4 mg solution for injection



* 2, 5, 6, 10, 25, 50, 5x 50

ONDANSETRON 4MG/2ML SOLUTION FOR INJECTION
PL 20223/0009

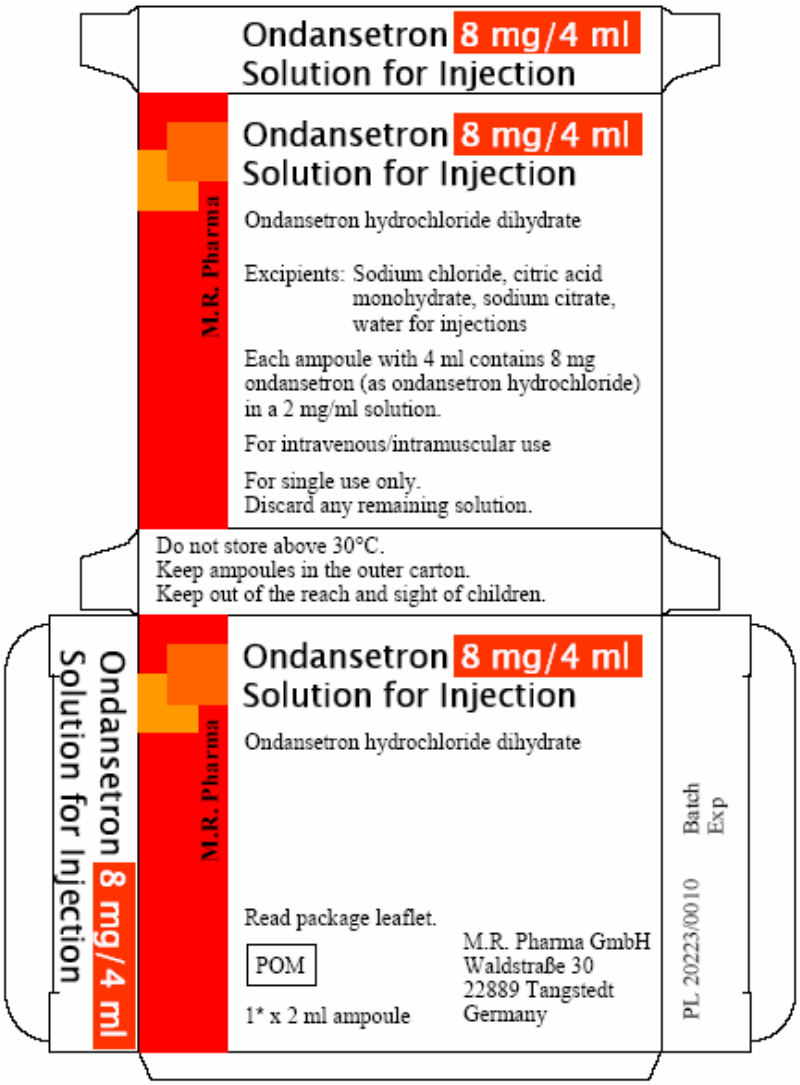
Label Ondansetron 4 mg solution for injection



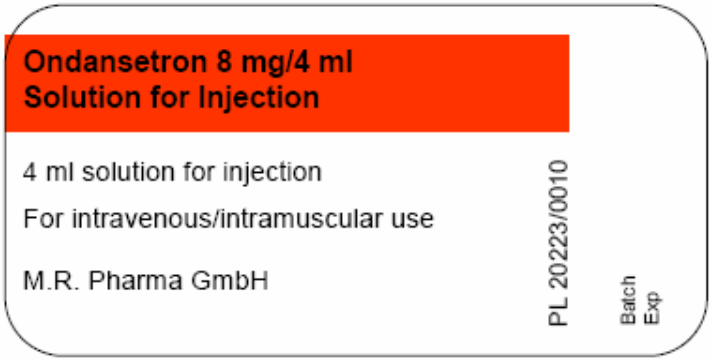
ONDANSETRON 8MG/4ML SOLUTION FOR INJECTION
PL 20223/0010

1.3.2 LABELLING

Outer box Ondansetron 8 mg solution for injection



* 2, 5, 6, 10, 25, 50, 5x 50

ONDANSETRON 8MG/4ML SOLUTION FOR INJECTION
PL 20223/0010

Label Ondansetron 8 mg solution for injection