Public Assessment Report

Ondansetron 4mg Film-coated Tablets
Ondansetron 8mg Film-coated Tablets

Ondansetron

PL 08553/0247
PL 08553/0248

Dr Reddy's Laboratory (UK) Ltd

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Lay Summary

The MHRA has granted Dr Reddy's Laboratories (UK) Ltd Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg Tablets and Ondansetron 8mg Tablets. These are prescription-only medicines (POM) for the treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults.

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist, its exact mechanism of action is unknown. The test product was considered the same as the original products Zofran 8mg Tablets based on the bioequivalence study submitted and no new safety issues arose as a result of this study. It was therefore judged that the benefits of taking Ondansetron 4mg Tablets and Ondansetron 8mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Ondansetron 4mg Tablets (PL 08553/0247) and Ondansetron 8mg Tablets (PL 08553/0248) on 21st November 2007.

These products are prescription only medicines indicated in the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults. Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist

The products are claimed to be generic medical products of Zofran® tablets (GlaxoSmithKline PLs 10949/0263-4) which were granted UK approval in May 1990.

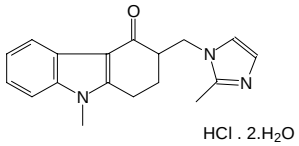
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

General information

The active substance is supplied by Dr Reddy's Laboratories Ltd.

Structure:



Description: White to off white powder

Molecular formula: $C_{18}H_{20}ClN_3O. 2H_2O$

Relative molecular mass: 365.9

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Ondansetron is stored in HDPE drums lined with double polyethene bags into a metal barrel with a seal. Relevant specifications controlled to Ph Eur and satisfactory certificates of analysis for the packaging components are provided. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 60 months.

DRUG PRODUCT

Other ingredients

The other ingredients found in these products are listed below. Appropriate justification for the inclusion of each excipient has been provided.

Lactose monohydrate
Cellulose, microcrystalline (E463)
Starch, pregelatinised
Silica, colloidal anhydrous
Sodium starch glycolate
Magnesium stearate (E470b)
Hypromellose (E464)
Talc (E553b)
Titanium dioxide (E171)
PEG 400
Iron oxide yellow (E172)

All the excipients are controlled to the Ph Eur monograph. Certificates of analysis for all excipients were provided and conformed to the specification. Magnesium stearate, used in the manufacture of Ondansetron 4mg and 8mg Tablets, is derived from a vegetable source; a certificate of TSE/BSE compliance of magnesium stearate from the supplier is provided.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data

have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container closure system
The tablets are packed in Al/PVC/PVdC clear and white opaque blister packs. Specifications are provided. Satisfactory Certificates of Analysis for the packaging materials were provided and packaging components conform to the food contact requirements in 2002/72/EC and are controlled to the Ph Eur monograph.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 30°C”.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

MEDICAL ASSESSMENT

Clinical Pharmacology

Ondansetron is a potent, selective 5HT3 receptor-antagonist. The mechanism of action of Ondansetron is not fully known. Cytotoxic Chemotherapy appears to cause release of 5HT in the small intestine, which initiates a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex.

Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. Activation of vagal afferents may result in the release of 5HT in the area postrema, located on the floor of the fourth ventricle. This may promote emesis through a central mechanism. Thus, the antiemetic effect of ondansetron is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.

Bioequivalence Study

The applicant has submitted a comparative pharmacokinetic study. The objective of this study was to evaluate the comparative bioavailability between Ondansetron Tablets 8 mg (manufactured by Dr Reddy's Laboratories Ltd) and Zofran™ Tablets 8mg (Glaxo SmithKline, UK Ltd).

This was a blinded, single dose, randomized, two-period, two-sequence, crossover study under fasting conditions. The study consisted of two treatment phases, separated by a wash out of 10 days. Twenty six healthy male volunteers entered the study. One subject was withdrawn due to illness prior to dosing in period of the study.

Blood samples were collected at frequent intervals during the study up to 24 hours post dosing. The plasma samples were subsequently analysed by a validate LCMS/MS method for ondansetron content. Safety data were collected for each subject that was assayed throughout the study by recording vital signs and reported adverse events.

Statistical evaluation for both test and reference products, were calculated for all pharmacokinetic parameters across all subjects analyzed. The following reported results are included: Geometric means of AUCs and Cmax for both test and reference products. Ratios of geometric means of test versus reference products for AUCs and Cmax. 90% confidence intervals of the above ratios. The main pharmakonetic findings are summarised in the tables below.

(Arithmetic mean data , n = 25)

Parameter	Ondansetron 8mg Tablets		Zofran 8 mg Tablets	
	Mean	SD	Mean	SD
C_{max}	36.703	11.529	35.142	11.070
T_{max}	2.23	0.84	2.17	0.64
$AUC_{(0-t)}$	249.695	82.640	227.792	62.775
$AUC_{(0-\infty)}$	262.776	92.049	238.657	66.535
$t_{1/2}$	5.54	1.40	5.41	1.45

(Geometric mean data, n = 25)

Parameter	Ondansetron 8mg Tablets	Zofran 8 mg Tablets
Cmax (ng/ml)	34.925	33.391
AUC(0-t)(ng.hr/ml)	237.683	219.152
AUC(0-∞)(ng.hr/ml)	249.027	229.266

Parameter	Mean Ratio (test/ref)	90% CI (%)
Cmax	104.43%	93.10% - 117.15%
AUC(0-t)	105.73%	97.53% - 114.61%
AUC(0-∞)	105.79%	97.77% - 114.47%

The 90% confidence intervals of the relative mean AUC and Cmax of the test to reference products for the measured data were within the 80-125% confidence intervals. The study demonstrated bioequivalence and there were no new safety concerns.

Efficacy
No new efficacy data are presented for this application and none is required. However the applicant has provided a critical and review of clinical trials published in the literature regarding the efficacy and safety of ondansetron.

Safety
No new safety data are provided or needed. But the applicant has provided a brief safety review of ondansetron. No new safety issues have been identified.

Summary Of Product Characteristics
The text of the proposed SPC was amended to be essentially the same as that of the cross-reference product licence.

Patient Information Leaflet
This was satisfactory.

Labelling
Full colour mock-ups were provided.

Discussion
The highly selective 5HT3 receptor-antagonists, including ondansetron, have been available in the UK for over 10 years. The use of ondansetron is well established. It has recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted. When used as indicated, ondansetron. has a favourable benefit-to-risk ratio. The hazard associated with ondansetron. appears to be low and acceptable when considered in relation to its therapeutic benefits.

Conclusion
Marketing Authorisations may be granted for these products.

Overall Conclusion and Risk/Benefit Analysis

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.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

Bioequivalence has been demonstrated between the applicant's Ondansetron Tablets and Zofran™ Tablets. Given that linear kinetics apply between the 4mg and 8mg tablets, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 4mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Zofran Tablets.

Risk/Benefit Analysis

The quality of the product 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. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 17th August 2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15th September 2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 7th April 2006 and on the medical assessment on 14th August 2007
4	The applicant provided further information in regard to the quality assessment on 17th October 2006 and on the medical assessment on 24th September 2007.
5	The application was determined on 21st November 2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Ondansetron 4mg film-coated Tablet contains ondansetron 4mg (as hydrochloride dihydrate) and 77.5mg of lactose.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light yellow, oval, biconvex, film-coated tablets embossed 'OND' on one side and '4' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

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 should be flexible in the range of 8-32mg 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 of ondansetron 1-2 hours prior to 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. An oral twice daily 4mg dose 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.

<u>Post operative nausea and vomiting</u>

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 in the prevention and treatment of post-operative nausea and vomiting in the elderly, however ondansetron is 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

Ondansetron film-coated Tablets are contraindicated in patients with a known hypersensitivity to ondansetron or any of the listed excipients.

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 precautions for use

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

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

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 there are no pharamcokinetic interactions when ondansetron is administered with alcohol, temazepam, 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 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

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The

incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data. The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

Immune system disorders
Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders
Very common: Headache.
Uncommon: Seizures, movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae.
Rare: Dizziness during i.v. administration, which in most cases is prevented or resolved by lengthening the infusion period..

Eye disorders
Rare: Transient visual disturbances (eg. blurred vision) during i.v. administration.
Very rare: Transient blindness predominantly during intravenous administration
The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

Cardiac disorders
Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Constipation.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests[#].
[#]These events were observed commonly in patients receiving chemotherapy with cisplatin.

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. The use of Ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic nature of ondansetron.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants
ATC code: A04AA01

Ondansetron is a potent, selective 5HT3 receptor-antagonist. The mechanism of action of Ondansetron is not fully known. Cytotoxic Chemotherapy appears to cause release of 5HT in the small intestine, which initiates a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex.

Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. Activation of vagal afferents may result in the release of 5HT in the area postrema, located on the floor of the fourth ventricle. This may promote emesis through a central mechanism. Thus, the antiemetic effect of ondansetron is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.

Ondansetron does not seem to 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
There is no additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, microcrystalline (E463)
Starch, pregelatinised
Silica, colloidal anhydrous
Sodium starch glycolate
Magnesium stearate (E470b)
Hypromellose (E464)
Talc (E553b)
Titanium dioxide (E171)
PEG 400
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVdC/Al blister strips in cardboard carton

Cartons of 2, 4, 6, 10, 15, 20, & 30 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

To help protect the environment, medicines should not be disposed of via wastewater or household waste. A pharmacist can advise on how to safely dispose of unwanted medicines.

7 MARKETING AUTHORISATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 08553/0247

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2007

10 DATE OF REVISION OF THE TEXT

21/11/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Ondansetron 8mg film-coated Tablet contains ondansetron 8mg (as hydrochloride dihydrate) and 7.2mg of lactose.
For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Dark yellow, oval, biconvex, film-coated tablets embossed 'OND' on one side and '8' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

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 should be flexible in the range of 8-32mg 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 of ondansetron 1-2 hours prior to 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. An oral twice daily 4mg dose 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 in the prevention and treatment of post-operative nausea and vomiting in the elderly, however ondansetron is 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

Ondansetron film-coated Tablets are contraindicated in patients with a known hypersensitivity to ondansetron or any of the listed excipients.
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 precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.
Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.
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 there are no pharamcokinetic interactions when ondansetron is administered with alcohol, temazepam, 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 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

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data. The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

Uncommon: Seizures, movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae.

Rare: Dizziness during i.v. administration, which in most cases is prevented or resolved by lengthening the infusion period.

Eye disorders

Rare: Transient visual disturbances (eg. blurred vision) during i.v. administration.

Very rare: Transient blindness predominantly during intravenous administration

The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

Cardiac disorders

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

Gastrointestinal disorders

Common: Constipation.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests[#].

[#]These events were observed commonly in patients receiving chemotherapy with cisplatin.

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. The use of Ipecacuanha, however, is not recommended as patients are unlikely to react to it due to the anti-emetic nature of ondansetron.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants

ATC code: A04AA01

Ondansetron is a potent, selective 5HT3 receptor-antagonist. The mechanism of action of Ondansetron is not fully known. Cytotoxic Chemotherapy appears to cause release of 5HT in the small intestine, which initiates a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex.

Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. Activation of vagal afferents may result in the release of 5HT in the area postrema, located on the floor of the fourth ventricle. This may promote emesis through a central mechanism. Thus, the antiemetic effect of ondansetron is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.

Ondansetron does not seem to 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
There is no additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Cellulose, microcrystalline (E463)
Starch, pregelatinised
Silica, colloidal anhydrous
Sodium starch glycolate
Magnesium stearate (E470b)
Hypromellose (E464)
Talc (E553b)
Titanium dioxide (E171)
PEG 400
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
PVC/PVdC/Al blister strips in cardboard carton
Cartons of 2, 4, 6, 10, 15, 20, & 30 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
To help protect the environment, medicines should not be disposed of via wastewater or household waste. A pharmacist can advise on how to safely dispose of unwanted medicines.

7 MARKETING AUTHORISATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL08553/0248

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2007

10 DATE OF REVISION OF THE TEXT

21/11/2007

Labels and Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ondansetron 4mg and 8mg film-coated Tablets

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ONDANSETRON FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Ondansetron film-coated Tablets contain ondansetron, which belongs to a group of medicines called serotonin (5HT3) antagonists.

Ondansetron film-coated Tablets are used for the treatment of nausea and vomiting induced by medicines used for the treatment of cancer, radiation therapy or surgical procedures. These medicines, can cause you to be sick or feel sick (nausea and vomiting).

2. BEFORE YOU TAKE ONDANSETRON TABLETS

Do not take Ondansetron film-coated Tablets
- If you are allergic to Ondansetron or any of the other ingredients of the tablets listed in Section 6 or Section 2 (Important information about some of the ingredients of Ondansetron film-coated Tablets)
- If you are pregnant or you are breast-feeding.

Taking special care with Ondansetron film-coated Tablets
You should consult your doctor before taking Ondansetron if you have:
- a blockage in your gut or you have severe constipation
- liver disease
- a condition known as phenylketonuria (deficiency of enzymes which break down phenylalanine).

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Are you taking any of the following medicines?
- Phenytoin (for seizures),
- Carbamazepine (for seizures, bi-polar disorder, shooting pains in the face – trigeminal neuralgia)
- Rifampicin (used in bacterial infections, for tuberculosis and leprosy treatment)
- Tramadol (for moderate to severe pain)

Please inform your doctor of these before taking Ondansetron.

Taking Ondansetron Tablets with food and drink

There are no special requirements for taking these tablets with food or drink.

Pregnancy and breast-feeding

Inform your doctor if you are pregnant or are likely to be. Do not take Ondansetron film-coated Tablets if you are likely to be pregnant.

Ondansetron probably passes into breast milk. Please avoid taking these tablets if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
These tablets are not likely to cause any effect on your ability to drive or use machines.

Important information about some of the ingredients of Ondansetron film-coated Tablets.
Lactose is an ingredient in these tablets. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ONDANSETRON FILM-COATED TABLETS

Your doctor will advise you on when and how many Ondansetron film-coated Tablets you should take. Always take Ondansetron film-coated Tablets as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Tablets should be swallowed with a glass of water.

For treatment of nausea and vomiting caused by cancer chemotherapy or radiotherapy:
The recommended adult dose is 8mg 1 to 2 hours before start of cancer therapy followed by 8mg 12 hours later. To prevent nausea and vomiting after 24 hours of cancer therapy, take 8mg twice daily for up to 5 days. The recommended dose for children is 4mg twice a day for up to 5 days after receiving cancer chemotherapy or radiotherapy.

To prevent nausea and vomiting after 24 hours of therapy, 4mg twice daily for up to 5 days is recommended. Please ensure that you take the tablets as recommended by your doctor.

For prevention of nausea and vomiting after surgical procedures:
The usual adult dose is 16mg one hour prior to anaesthesia followed by two further 8mg doses 8 hours apart.

Patients with liver problems
If you have liver problems, your dose of Ondansetron film-coated Tablets should not exceed 8mg per day. If you are taking or have taken tests to check your liver function, Ondansetron film-coated Tablets may affect the results of these tests.

If you take more Ondansetron film-coated Tablets than you should
If you have accidentally taken more tablets than you should, contact your doctor or the nearest hospital immediately. Take this leaflet and the pack of Ondansetron film-coated Tablets with you, if you can.

If you forget to take Ondansetron film-coated Tablets
If you forget to take the tablets, take one as soon as possible. If you have missed a dose but do not feel sick or do not vomit, take the next at the usual time recommended by your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you stop taking Ondansetron film-coated Tablets
No special precautions are necessary when you stop taking Ondansetron film-coated Tablets

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ondansetron film-coated Tablets may cause side effects, although not everybody gets them. Many side effects are usually mild and the side effects and go away when you stop taking Ondansetron film-coated Tablets. The side effects include:

Very common (seen in more than 1 in10 people):
Headache

Common (seen in less than 1 in 10 people but not in more than 1 in 100 people):
Sensation of warmth or flushing,
Constipation

Uncommon (seen in less than 1 in 100 people but not in more than 1 in 1000 people):
Fits, abnormal muscle movements or muscle stiffness, upward rolling of eyes, slow or irregular heartbeat. Contact your doctor as soon as possible if any of these side effects are seen.
Hiccups

Rare (seen in less than 1 in 1000 people but not in more than 1 in 10,000 people):
Hypersensitivity reactions including sudden chest pain, wheeziness, swelling of eyelids, face, lips or tongue, skin rashes, hives or red spots. Contact your doctor immediately if any or all of these signs are seen. Rarely dizziness has been observed but only when Ondansetron is administered by the intravenous route.

Very rare (seen in less than 1 in 10,000 people):
Temporary loss of vision may occur very rarely and is seen mostly during intravenous administration. It usually goes away in about 20 minutes.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE ONDANSETRON FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not store Ondansetron film-coated Tablets above 30°C.

Keep Ondansetron film-coated Tablets in its original pack.

Do not use Ondansetron film-coated Tablets after the expiry date. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ondansetron film-coated Tablets contain

The active substance is Ondansetron (4mg or 8mg).

The other ingredients are: microcrystalline cellulose, lactose, pregelatinized starch, anhydrous colloidal silica, magnesium stearate, hypromellose, talc, titanium dioxide, PEG400 and iron dioxide.

What Ondansetron film-coated Tablets look like and contents of the pack

Ondansetron 4mg film-coated Tablets are light yellow oval, biconvex, film-coated tablets embossed 'OND' on one side and '4' on other side. Ondansetron 8mg film-coated Tablets are dark yellow, oval, biconvex, film-coated tablets embossed 'OND' on one side and '8' on other side.

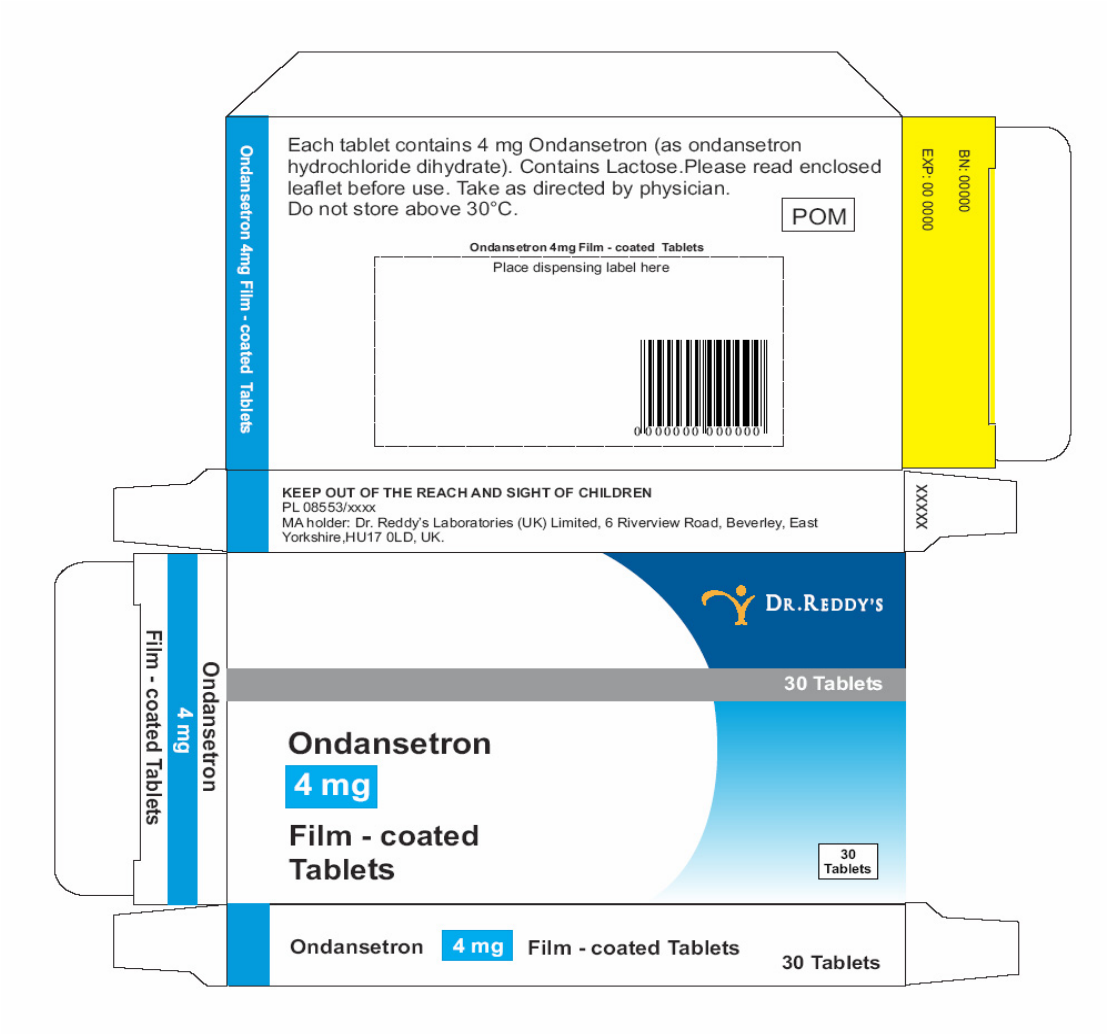
Ondansetron film-coated Tablets are packed in blister strips in cartons containing 2, 4, 6, 10, 15, 20 or 30 tablets. Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer

Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD, UK.

Ondansetron 4mg film-coated Tablets: PL08553/0247
Ondansetron 8mg film-coated Tablets PL08553/0248

Date of preparation: 09/2007
Component Code
Dr Reddy's Laboratories (UK) Ltd.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Each tablet contains 4 mg Ondansetron (as ondansetron hydrochloride dihydrate). Contains Lactose.Please read enclosed leaflet before use. Take as directed by physician.
Do not store above 30°C.
POM
Ondansetron 4mg Film - coated Tablets
Place dispensing label here
BN: 00000
EXP: 00 0000
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
PL 08553/xxxx
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XXXX
DR.REDDY'S
30 Tablets
Ondansetron
4 mg
Film - coated Tablets
Ondansetron
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30 Tablets
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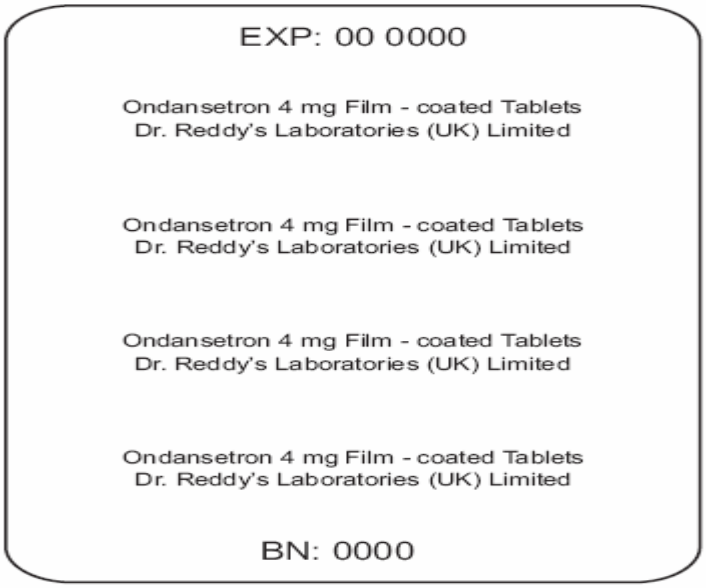
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Ondansetron 4 mg Film - coated Tablets
Dr. Reddy's Laboratories (UK) Limited
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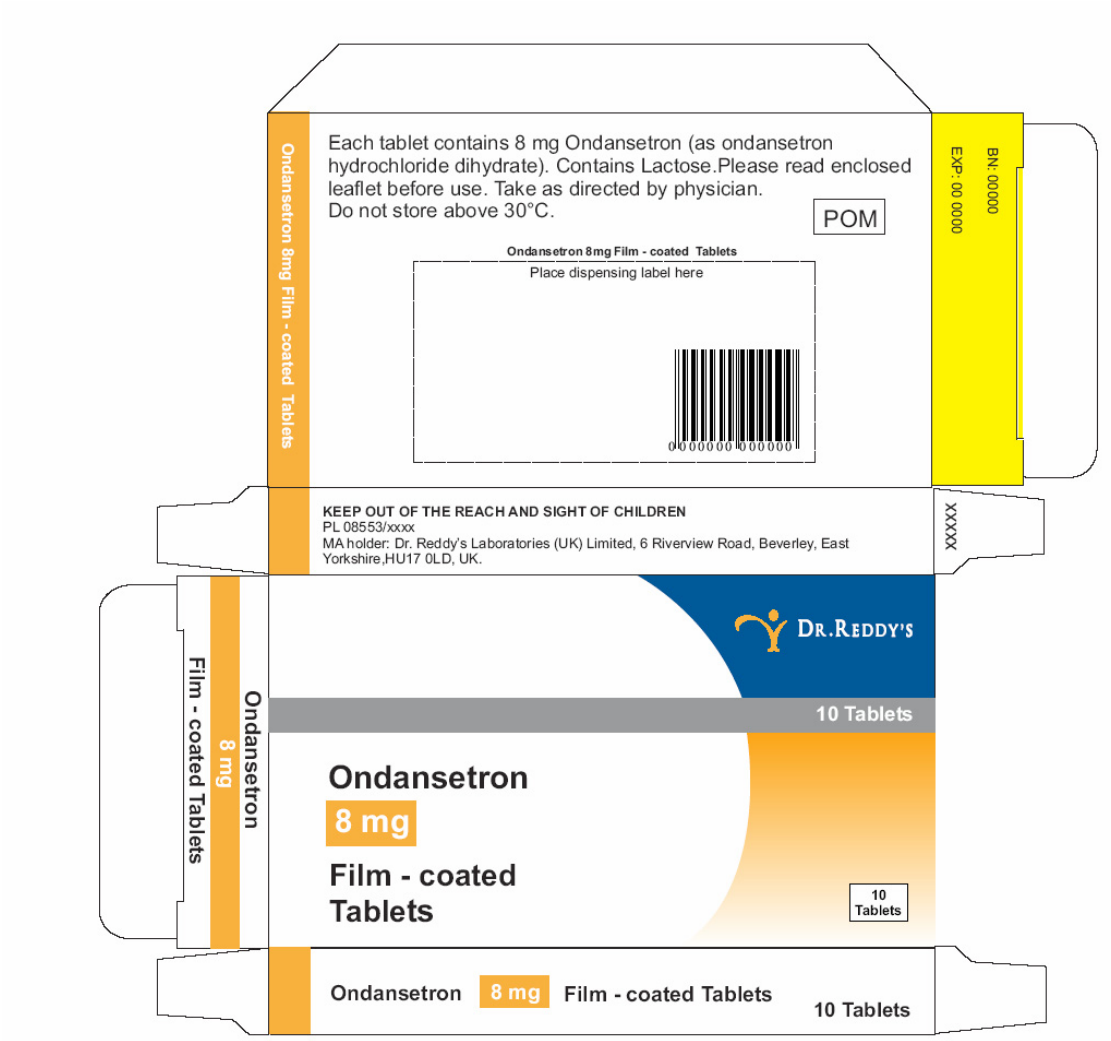
Ondansetron 8mg Film - coated Tablets
Each tablet contains 8 mg Ondansetron (as ondansetron hydrochloride dihydrate). Contains Lactose.Please read enclosed leaflet before use. Take as directed by physician.
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POM
Ondansetron 8mg Film - coated Tablets
Place dispensing label here
BN: 00000
EXP: 00 0000
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
PL 08553/xxxx
MA holder: Dr. Reddy's Laboratories (UK) Limited, 6 Riverview Road, Beverley, East Yorkshire,HU17 0LD, UK.
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DR.REDDY'S
10 Tablets
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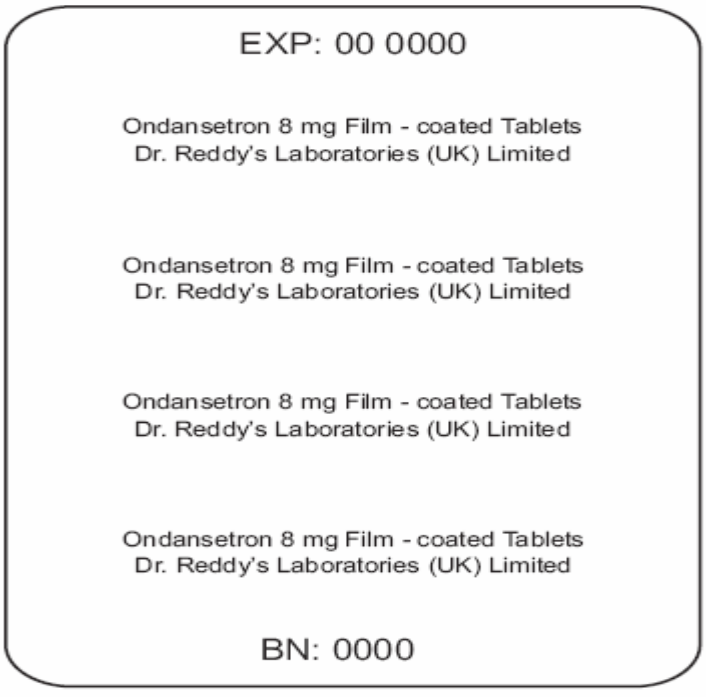
10 Tablets
Ondansetron 8 mg Film - coated Tablets 10 Tablets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Ondansetron 8 mg Film - coated Tablets
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