ONDANSETRON 4MG ORODISPERSIBLE TABLETS
PL 14894/0361
PL 14894/0363
PL 14894/0365
PL 14894/0411

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LAY SUMMARY

The MHRA granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg Orodispersible Tablets (PL 14894/0361, PL 14894/0363, PL 14894/0365 and PL 14894/0411) and Ondansetron 8mg Orodispersible Tablets (PL 14894/0362, PL 14894/0364, PL 14894/0366 and PL 14894/0412). These are prescription-only medicines (POM) for the prevention of nausea or vomiting as a result of chemotherapy/radiotherapy or after an operation.

Ondansetron Orodispersible Tablets contain the active ingredient ondansetron, which is an antiemetic medicine.

The test product was considered the same as the reference products Zofran™ Melt 4mg and 8mg Tablets (Glaxo Wellcome UK Ltd., UK) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ondansetron 4mg and 8mg Orodispersible Tablets outweigh the risks; hence Marketing Authorisations have been granted.

ONDANSETRON 4MG ORODISPERSIBLE TABLETS
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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 Orodispersible Tablets (PL 14894/0361, PL 14894/0363, PL 14894/0365 and PL 14894/0411) and Ondansetron 8mg Orodispersible Tablets (PL14894/0362, 14894/0364, 14894/0366 and 14894/0412) on 15th August 2007. The products are prescription-only medicines.

These are two strengths of Ondansetron, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, and have been shown to be generic medicinal products of the original, Zofran® 4mg and 8mg Orodispersible Tablets (GlaxoSmithKline Pharma A/S Denmark). The originator products have been have been authorised in the EU since 1990 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient ondansetron, a potent, highly selective serotonin ($5HT_3$) 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. 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 4mg and 8mg Orodispersible Tablets are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults.

These applications were submitted at the same time and depend on the bioequivalence study comparing the applicant's 8mg product with the reference product Zofran® Zydis Lingual 8mg Orodispersible Tablets (GlaxoSmithKline Co., Germany). Consequently, all sections of this Scientific Discussion refer to both 4mg and 8mg products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

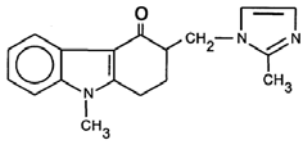
Ondansetron

INN: Ondansetron

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

CAS No: 99614-02-5

Structural Formula:



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

Molecular weight: 293.36

Physical form: Non-hygroscopic white to off-white powder.

Solubility: Soluble in chloroform and acetic acid.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance ondansetron.

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

An impurity profile for the drug substance has been provided and the impurities described are identical to those in the Ph.Eur.monograph for Ondansetron hydrochloride.

Active ondansetron is stored in clear double polythene bags. The inner and outer polythene bag is tied separately. The bag is kept in a high density polyethylene (HDPE) container sealed with a tamper proof lid. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

Appropriate stability data have been generated supporting a retest period of three years.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients, namely magnesium carbonate heavy, crospovidone, mannitol, magnesium stearate, aspartame, sodium saccharine, talc, colloidal anhydrous silica, flavour mangora 10877-31 and flavour frescofort 60470-31. All excipients used comply with their respective Ph.Eur monograph, with the exception of mannitol (which is controlled to a British Pharmacopoeia monogragh) and flavour mangora 10877-31 and flavour frescofort 60470-31 which are controlled to in-house specifications.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.
With the exception of magnesium stearate, none of the excipients used contain material of animal or human origin. The manufacturer of magnesium stearate has provided a TSE certificate of suitability.

Dissolution and impurity profiles

Dissolution profiles for both strengths of drug product were found to be similar to the originator products marketed in various European countries. The data demonstrates that the dissolution specification is acceptable. The impurity profiles for the drug product are the same as those described for the drug substance.

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

Product is packaged in either cold form blister laminate composed of aluminium foil and polyvinyl chloride (PVC) or aluminium strip packs composed of plain aluminium foil laminated with low density polyethylene (LDPE). Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 10 and 30 tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees” and “Store in original container”.

Conclusion

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

Ondansetron 4mg and 8mg Orodispersible Tablets have been shown to be generic medicinal products of Zofran Melt 4mg and 8mg Orodispersible Tablets. The proposed drug products correspond to the current EU definition of a generic product as they comply with the criteria of having the same qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence as the reference product.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

General
Ondansetron is used 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. These indications are consistent with those of the cross referenced product licences.

Dose & Dose Schedule
These are in line with those of the cross referenced product licence.

CLINICAL PHARMACOLOGY

Pharmacodynamics
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. 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.

Pharmacokinetics
Following oral administration of ondansetron, absorption is rapid with maximum peak plasma concentrations of about 30ng/ml being attained and achieved in approximately 1.5 hours after an 8 mg dose. The syrup and tablet formulations are bioequivalent and have an absolute oral bioavailability of 60%. The disposition of ondansetron following oral, intravenous and intramuscular dosing is similar with a terminal elimination half-life of approximately 3 hours and a steady-state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%) and 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 the pharmacokinetics of ondansetron. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

In patients with renal impairment (creatinine clearance >15 ml/min), systemic clearance and volume of distribution are reduced, 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.

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32h) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

Bioequivalence

The applicant has submitted a comparative pharmacokinetic study. This was a blinded, single dose, randomized crossover study. The objective of this study was to evaluate the comparative bioavailability between Ondansetron Orodispersible Tablets 8 mg (Ranbaxy Ltd, India) as the Test product (A) and Zofran™ Zydis Lingual 8mg Tablets (Glaxo SmithKline Ltd, Germany) as the Reference Product (B) in 31 healthy male subjects under fasting conditions with one week wash out period. Blood samples were collected at frequent intervals for up to 24 hours post-dose.

Analysis of variance (ANOVA) has been performed on pharmacokinetic parameters (C_{max}, $AUCO_{0-t}$, and $AUC_{o-\infty}$, for log (natural) - transformed data using general linear model procedures of SAS system. The 90% confidence interval for the ratios of $C_{max,}$ AUC_{o-t} and $AUC_{o-\infty}$ has been calculated.

The ANOVA model has been employed which included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. The 90% confidence intervals for the difference between drug formulation least-squares means (LSM) have been calculated for the In-transformed pharmacokinetic parameters, C_{max}, AUC_{0-t}, and $AUC_{o-\infty}$. The results for Ondansetron in the plasma for the log-transformed main pharmacokinetic findings are summarised in the tables below.

Parameters	C_{max} n mL		T_{max} h		AUC_{O-t} n .h/mL		AUCo∞ n .h/mL	
	B '	A	B	A	B	A	B	A
Mean	32.8227	31.9672	1.9446	2.1245	232.5837	231.6637	250.3993	250.9682
SD	13.5520	13.1413	0.4556	0.4845	122.7507	118.9159	143.0578	135.7880
Min	15.1250	9.5480	0.6600	1.0000	94.3347	45.0293	97.6938	48.4915
Max	78.9710	70.6030	3.0000	3.0000	1732.1044	636.7601	851.7737	723.5002
N	31	31	31	31	31	131	31	31

B: ZOFRAN Zydis Lingual 8 mg tablets manufactured by G1axoSmithKline Co, Germany. A:Ondansetron orodispersible tablets 8 mg of Ranbaxy Laboratories Limited, India.

Parameter	**90% Confidence Intervals**
C_{max}	95.97% (90.62-101.63%)
AUC_{o-t}	97.09% (91.03-103.56%)
$AUC_{o-\infty}$	98.00% (91.77-104.64%

Adverse events included stomach ache, sore throat, dizziness, nausea, flushing and headache. All were mild in severity. None of the adverse events had a significant impact on the safety of the subjects or on the integrity of the study results. No serious adverse events were reported during the conduct of this study.
The 90% confidence intervals of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test to reference products for measured data and data adjusted for measured drug content were within the 80-125% range. Therefore, Ranbaxy Ltd. test drug of Ondansetron Orodispersible Tablets 8mg , exhibited equivalent rate and extent of absorption to Zofran™ Zydis Lingual 8mg tablets 8mg, in healthy volunteers, after a single oral-dose, under fasting conditions and therefore, they are bioequivalent drug products.

The essentially linear pharmacokinetics ondansetron, particularly at this relatively low dose range, makes it likely that the lower-dose of Ondansetron formulation also is bioequivalent to the corresponding marketed brand formulation although bioequivalence has not been assessed explicitly.

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.

EXPERT REPORT
A satisfactory Clinical Expert Report has been submitted with appropriate CV.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory. The text of the SPC is essentially the same as that of the cross-reference product licence.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
The applicant appears to have demonstrated bioequivalence. Marketing authorisations should be granted for these products

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 4mg and 8mg Orodispersible Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Ondansetron 8mg Orodispersible Tablets and Zofran 8mg Zydis Lingual (GlaxoSmithKline, Germany). 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 the cross-reference product.

RISK BENEFIT ASSESSMENT

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. Extensive clinical experience with ondansetron is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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PL 14894/0364
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PL 14894/0412

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 23rd December 2004.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 3rd February 2005.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 17th August 2006 and further information relating to the quality dossiers on 29th September 2005 and 17th August 2006.
4	The applicant responded to the MHRA's requests, providing further information on 22nd September 2006 for the clinical sections, and again on 30th June 2006 and 27th March 2007 for the quality sections.
5	The applications were determined on 15th August 2007.

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

PL 14894/0361, PL 14894/0363, PL 14894/0365 and PL 14894/0411

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of ondansetron.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible Tablet

White to off-white, circular, flat beveled tablets debossed with '**02**' one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Place the tablet in the mouth where it can be allowed to dissolve or swallow whole with some fluid.

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 and selected from rectal, oral (as tablets or syrup) intravenous or intramuscular administration.

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

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

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

Highly emetogenic chemotherapy (e.g. high dose cisplatin) should be treated by rectal, intravenous or intramuscular administration.

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

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

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

POST OPERATIVE NAUSEA AND VOMITING (PONV)

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

For oral administration: 16 mg one hour prior to anaesthesia. Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg 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 PONV in the elderly, however, ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

For both indications

Patients with renal impairment:
No special requirements.

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 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 tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

Patients with signs of subacute intestinal obstruction should be monitored following administration.

Caution in patients with phenylketonuria.

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 ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

Ondansetron is metabolized by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolizing 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 indicated 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 the 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

None reported

4.8 UNDESIRABLE EFFECTS

There have been rare reports of immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

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.

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 transient, asymptomatic increases in liver function tests.

Rare cases of transient visual disturbances (e.g. blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron.

4.9 OVERDOSE

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known.

Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

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

5.2 PHARMACOKINETIC PROPERTIES

Following oral administration of ondansetron, absorption is rapid with maximum peak plasma concentrations of about 30ng/ml being attained and achieved in approximately 1.5 hours after an 8 mg dose. The tablet formulations has an absolute oral bioavailability of 60%. The disposition of ondansetron following oral, intravenous and intramuscular dosing is similar with a terminal elimination half-life of approximately 3 hours and a steady-state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%) and 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 the pharmacokinetics of ondansetron.

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown a slight but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5h) 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).

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 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 (0.1 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 ml/min), systemic clearance and volume of distribution are reduced, 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.

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32h) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

5.3 PRECLINICAL SAFETY DATA
No additional data.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Intragranular
Magnesium carbonate heavy
Crospovidone
Mannitol (E421)
Magnesium stearate

Extragranular
Crospovidone
Mannitol (E421)
Aspartame (E951)
Sodium saccharine
Talc
Colloidal anhydrous silica
Magnesium stearate
Flavour Mangora 10877-31 (Maltodextrins (maize), Arabic gum (E414, Ascorbic acid (E330) and Butylated hydroxyanisol (BHA) (E320))
Flavour Frescofort 60470-31 (Maltodextrins (maize) and Starch modified (E1450) (Waxy Maize))

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25ºC. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Ondansetron Orodispersible Tablets are packaged in either:
1) cold form blister laminate composed of aluminium foil, PVC and polyamide.
2) aluminium strip pack of plain aluminium foil laminated with LDPE.

Pack sizes of 10 and 30 Tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirement

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton Street
London W1K 6TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894 /0361
PL 14894 /0363
PL 14894 /0365
PL 14894 /0411

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/08/2007

10 DATE OF REVISION OF THE TEXT

15/08/2007

PL 14894/0362, PL 14894/0364, PL 14894/0366 and PL 14894/0412

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg of ondansetron.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible Tablet
White to off-white, circular, flat beveled tablets debossed with '**01**' one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Place the tablet in the mouth where it can be allowed to dissolve or swallow whole with some fluid.

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 and selected from rectal, oral (as tablets or syrup) intravenous or intramuscular administration.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral 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 (e.g. high dose cisplatin) should be treated by rectal, intravenous or intramuscular administration.

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

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

Children:

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

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

POST OPERATIVE NAUSEA AND VOMITING (PONV)
Adults:
For the prevention of PONV: Ondansetron may be administered either 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 PONV in the elderly, however, ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

For both indications

Patients with renal impairment:
No special requirements.

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

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

4.3 CONTRAINDICATIONS
Hypersensitivity to any component of the tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

Patients with signs of subacute intestinal obstruction should be monitored following administration.

Caution in patients with phenylketonuria.

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 ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

Ondansetron is metabolized by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolizing 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 indicated 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 the 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

None reported

4.8 UNDESIRABLE EFFECTS

There have been rare reports of immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

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.

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 transient, asymptomatic increases in liver function tests.

Rare cases of transient visual disturbances (e.g. blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron.

4.9 OVERDOSE

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known.

Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

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

5.2 PHARMACOKINETIC PROPERTIES

Following oral administration of ondansetron, absorption is rapid with maximum peak plasma concentrations of about 30ng/ml being attained and achieved in approximately 1.5 hours after an 8mg dose. The tablet formulations has an absolute oral bioavailability of 60%. The disposition of ondansetron following oral, intravenous and intramuscular dosing is similar with a terminal elimination half-life of approximately 3 hours and a steady-state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%) and 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 the pharmacokinetics of ondansetron.

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown a slight but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5h) 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).

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 ml/min), systemic clearance and volume of distribution are reduced, 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.

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32h) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

5.3 PRECLINICAL SAFETY DATA
No additional data.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Intragranular

Magnesium carbonate heavy
Crospovidone
Mannitol (E421)
Magnesium stearate

Extragranular

Crospovidone
Mannitol (E421)
Aspartame (E951)
Sodium saccharine
Talc
Colloidal anhydrous silica
Magnesium stearate
Flavour Mangora 10877-31 (Maltodextrins (maize), Arabic gum (E414, Ascorbic acid (E330) and Butylated hydroxyanisol (BHA) (E320))
Flavour Frescofort 60470-31 (Maltodextrins (maize) and Starch modified (E1450) (Waxy Maize))

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25ºC. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Ondansetron Orodispersible Tablets are packaged in either:

1) cold form blister laminate composed of aluminium foil, PVC and polyamide.

2) aluminium strip pack of plain aluminium foil laminated with LDPE.

Pack sizes of 10, 15 and 30 Tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirement

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited

20 Balderton Street

London W1K 6TL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894 /0362
PL 14894 /0364
PL 14894 /0366
PL 14894 /0412

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/08/2007

10 DATE OF REVISION OF THE TEXT

15/08/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

ONDANSETRON 4 mg ORODISPERSIBLE TABLETS
ONDANSETRON 8 mg ORODISPERSIBLE TABLETS

(ONDANSETRON)

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

In this leaflet:

The name of the medicine is Ondansetron 4 mg or 8 mg Orodispersible Tablets (also referred to as Ondansetron Orodispersible Tablets throughout this leaflet). Ondansetron tablets are available in two strengths: 4 mg or 8 mg.

Marketing Authorisation Holder: Ranbaxy (UK) Limited, 20 Balderton Street, London W1K 6TL, UK

Manufacturer: Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co-Tipperary, Republic of Ireland.

1. What Ondansetron Orodispersible Tablets Are And What They Are Used For

The active ingredient is Ondansetron.

Ondansetron 4 mg Orodispersible Tablets are white to off-white, circular, flat tablets debossed with '**02**' on one side and plain on the other side.

Ondansetron 8 mg Orodispersible Tablets are white to off-white, circular, flat tablets debossed with '**01**' on one side and plain on the other side.

Each tablet also contains inactive ingredients: magnesium carbonate heavy, crospovidone, mannitol (E421), magnesium stearate, aspartame (E951), sodium saccharine, talc and colloidal anhydrous silica. The tablets also contain the flavourings mangora 10877-31, which contains Maltodextrins (maize), Arabic gum (E414), Ascorbic acid (E330) and Butylated hydroxyanisol (BHA) (E320) and frescofort 60470-31, which contains Maltodextrins (maize) and Starch modified (E1450).

Ondansetron Orodispersible Tablets are available in pack sizes of 10, 15 or 30 tablets.

Not all pack sizes may be marketed.

Ondansetron belongs to the class of medicines called antiemetic and antinauseants.

Ondansetron Orodispersible Tablets are used for one or more of the following:

- Nausea and vomiting as a result of chemotherapy or radiotherapy
- Prevention of nausea or vomiting after an operation

2. Before You Take Ondansetron Orodispersible Tablets

Do not take Ondansetron Orodispersible Tablets if any of the following apply to you.

Take special care with Ondansetron Orodispersible Tablets if:

- You have previously had an allergic reaction to ondansetron or to any of the tablet ingredients listed above. (An allergic reaction may include rash, itching, swelling of face, lips, hands/feet or breathing difficulties)
- You are allergic to other serotonin blocking drugs
- You have problems with your liver your doctor may reduce the dose
- You have recently been diagnosed with a bowel obstruction
- You have a condition called phenylketonuria (disorder of protein in the body)

Please consult your doctor if any of the above were applicable to you in the past.

Talk to your doctor before taking Ondansetron Orodispersible Tablets if you are taking any of the following medicines:

- Phenytoin or Carbamazepine (used for the treatment of epilepsy)
- Rifampicin (used for the treatment tuberculosis)
- Tramadol (used for the treatment of pain relief)

If you need to undergo an operation or anaesthetic, tell the doctor if you are already taking this medicine.

Pregnancy and Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Ondansetron rarely affects your ability to drive or operate machinery. Make sure you know how you react to ondansetron before you drive, use machines or engage in anything that could be dangerous if you are not alert.

Taking other medicines

Please inform your doctor or pharmacist if you are taking, or have recently taken,

any other medicines, even those not prescribed but bought/obtained without a prescription.

Important information about some of the ingredients of Ondansetron Orodispersible Tablets

Your medicine contains an inactive ingredient called aspartame (E951) which contains a source of phenylalanine and may be harmful for people with phenylketonuria. Your medicine also contains Butylated hydroxyanisole (E320) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

3. How To Take Ondansetron Orodispersible Tablets

Take your medicine as instructed by your doctor. Do not take more than the doctor has told you to. Always read the enclosed leaflet carefully before you take Ondansetron Orodispersible Tablets. Your pharmacist or doctor can help if you are not sure.

The amount of nausea and vomiting differs between individuals and depends somewhat on the strength of chemotherapy, radiotherapy or anaesthetic used.

- The starting dose of Ondansetron Orodispersible Tablets for patients having chemotherapy or radiotherapy is 8 mg one to two hours before treatment, followed by 8 mg twelve hours later. In order to stop delayed sickness your doctor will usually instruct you to take 8 mg twice a day for up to 5 days after the treatment.
- If you are having an operation you may be given 8 mg or 16 mg one hour before the anaesthetic. If you have 8 mg initially the doctor may prescribe you another 8 mg dose at eight hourly intervals.

Children need their dose calculated carefully by the doctor based on their body weight. Do not alter their prescribed dose unless the doctor instructs you to do so.

Place the tablet in the mouth where it can be allowed to dissolve or swallow whole with some fluid.

Take your tablets as directed and for as long as directed; do not stop them, even if you feel better, as otherwise the symptoms may return.

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

If you forget to take Ondansetron Orodispersible Tablets at the right time, take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.

If you have taken more Ondansetron Orodispersible Tablets than you should, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

4. Possible Side Effects

Like all medicines, Ondansetron Orodispersible Tablets can have side effects.

If any of the following happen, stop taking Ondansetron Orodispersible Tablets and tell your doctor immediately or go to the casualty department at your nearest hospital.

- Rashes, hives, itching, chest constriction, shortness of breath or swelling of face, lips, hands/feet, fainting, high temperature

These are very serious side effects. If you have them you may have had a serious allergic reaction or other type of reaction to Ondansetron. You may need urgent medical attention or hospitalization.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Chest pain, irregular, fast or slow heart beat, dizziness
- Jerking movements/muscle spasms or upward rolling of eyes
- Fits

Tell your doctor if you notice any of the following:

- Headache, blurred vision
- Feeling of flushing or warmth, hiccups
- Constipation

There may be changes in certain laboratory tests

- Abnormal liver function - tell your doctor if you experience any nausea, reduced appetite, excessive tiredness, abdominal pain or jaundice

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

5. Storing Ondansetron Orodispersible Tablets

Do not store above 25°C. Store in the original package.

Keep out of the reach and sight of children.

Do not take after the expiry date on the labeling.

If your doctor tells you to stop taking the tablets, please take them back to the pharmacist.

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.

This leaflet was prepared in August 2006.

POM

LABELLING

PL 14894/0361, PL 14894/0363, PL 14894/0365 & PL 14894/0411

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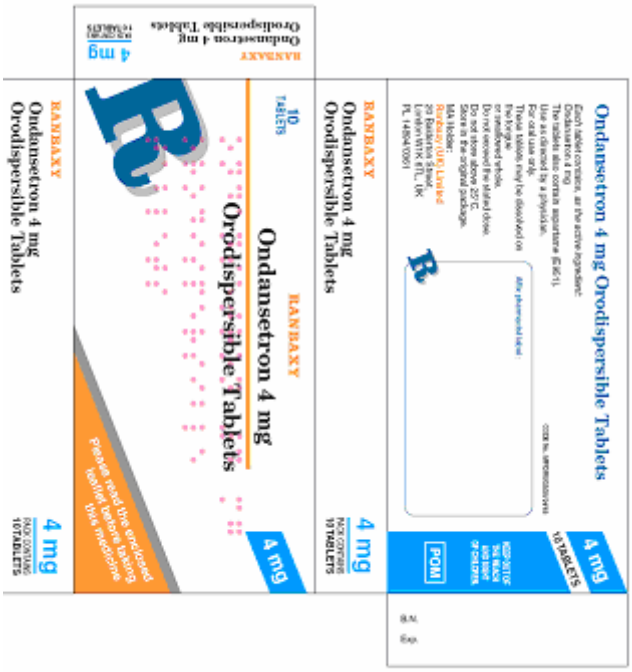
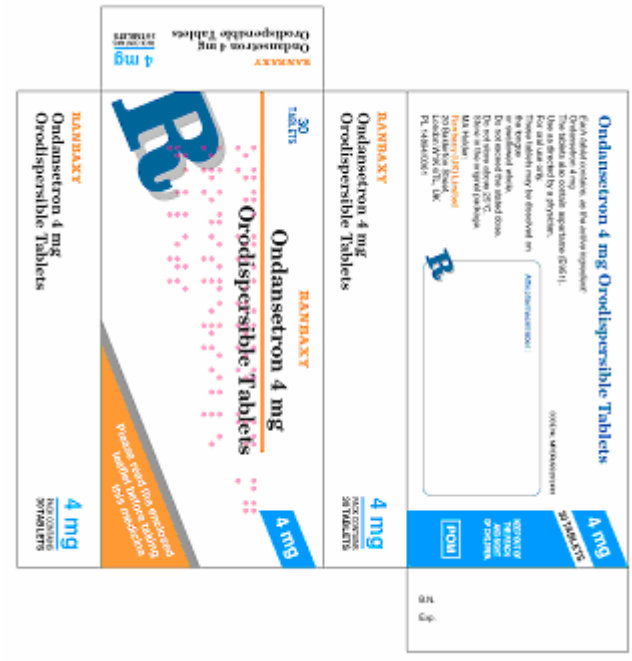
ONDANSETRON 4MG ORODISPERSIBLE TABLETS (10 TABLETS)



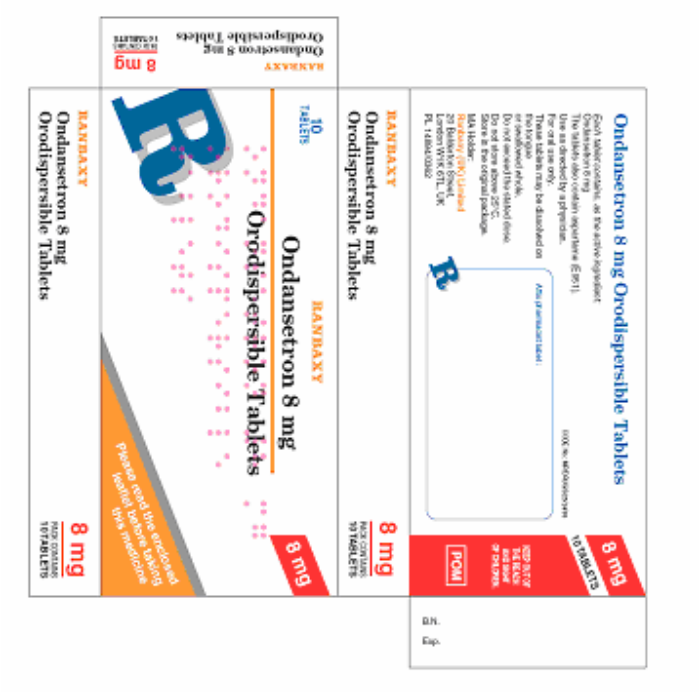
ONDANSETRON 4MG ORODISPERSIBLE TABLETS (30 TABLETS)



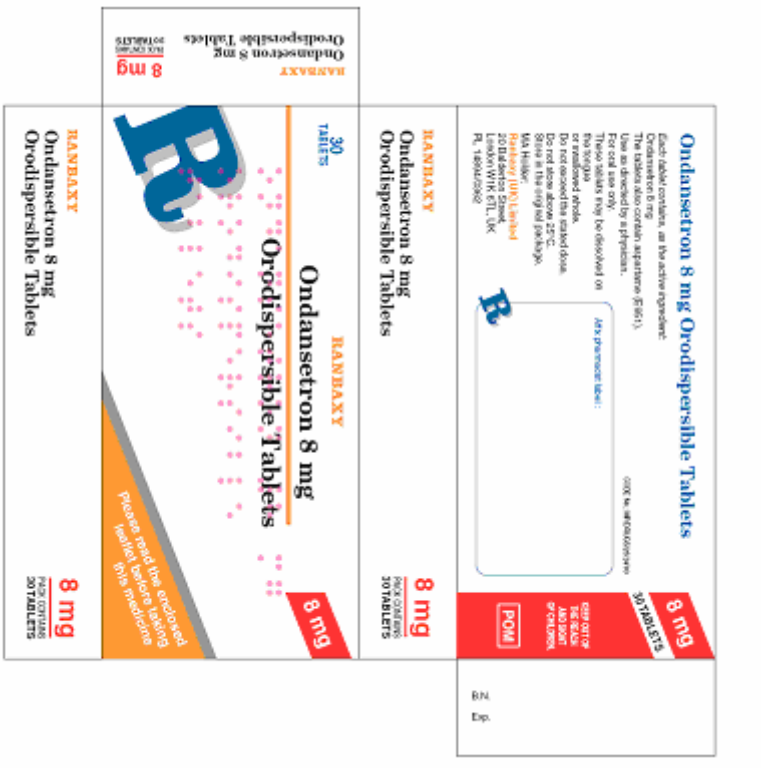
FOIL
ONDANSETRON 4MG ORODISPERSIBLE TABLETS

PL 14894/0362, PL 14894/0364, PL 14894/0366 & PL 14894/0412

CARTON-
ONDANSETRON 8MG ORODISPERSIBLE TABLETS (10 TABLETS)



CARTON-
ONDANSETRON 8MG ORODISPERSIBLE TABLETS (30 TABLETS)



FOIL
ONDANSETRON 8MG ORODISPERSIBLE TABLETS