

Public Assessment Report

Ondansetron 4mg Orodispersible Tablet Ondansetron 8mg Orodispersible Tablet

Ondansetron

PL 00289/0685

PL 00289/0686

PL 00289/0687

PL 00289/0688

TEVA UK Ltd

Table of Contents

	Page
Lay Summary	2
Scientific Discussion	3
Overall Conclusion And Risk Benefit/Analysis	10
Steps Taken During Assessment	11
Summary of Product Characteristics	13
Labels and Leaflet	28

Lay Summary

The MHRA today granted TEVA UK Limited Market Authorisations (licences) for the medicinal products Ondansetron 4mg and 8mg Orodispersible Tablets. This is a prescription only medicine (POM) for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting.

These products contain the active ingredient ondansetron. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ondansetron 4mg or 8mg Orodispersible Tablets outweighs the risks hence Marketing Authorisations were granted.

Scientific Discussion

INTRODUCTION

This Public Assessment report is based on the assessment report for National applications for Ondansetron 4mg Orodispersible Tablets (PL 00289/0685) and a duplicate application (PL 00289/0687) and Ondansetron 8mg Orodispersible Tablets (PL 00289/0686) and a duplicate application (PL 00289/0688). Market Authorisations were granted in the UK on 13th August 2007.

The applications claimed to be a generic medical product under 10.1 of Directive 2001/83/EC of Zofran 4mg and 8mg Orodispersible Tablets first authorised in Denmark in 1990. The UK marketed products are Zofran Melt 4mg and 8mg Orodispersible Tablets (PL 10949/0263-0264) authorised to Glaxo Wellcome UK Ltd, first licensed in the UK on 3rd April 1998.

These products contain the active ingredient ondansetron which is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting. Ondansetron is a potent, highly selective 5HT₃ receptor-antagonist.

The precise mode of action of ondansetron 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 neurones located both in the peripheral and central nervous system.

These applications were submitted at the same time and both depend on two bioequivalence studies which compared the products with the reference products Zofran® Melt 8 mg, orodispersible tablets & Zofran® 8 mg, film-coated tablets.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Ondansetron (base) is a non-hygroscopic white to off-white powder sparingly soluble in dichloromethane, soluble in ethanol and methanol, slightly soluble in acetonitrile and insoluble in water. It is used as the racemate.

Nomenclature

rINN: Ondansetron

(±)-1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazole-4-one

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

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

Structure

C₁₈H₁₉N₃O

MW: 293.4

CAS Number: 99614-02-5

The active substance has a European Drug Master File and an appropriate letter of access was provided.

An appropriate specification was provided by the active substance manufacturer and satisfactory batch data to demonstrate that ondansetron met the specification.

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

Active ondansetron is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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 24 months, with no specific storage instructions.

DRUG PRODUCT

Composition of the Drug Product

Mannitol 60

Basic butylated methacrylate copolymer (Eudragit E100)

Precipitated silica, hydrated

Strawberry flavour (maltodextrin, arabic gum, lactose, triethyl citrate)

Aspartame

Crospovidone

Magnesium stearate

All excipients included in the tablets comply with relevant Ph Eur monographs, except for the precipitated silica hydrated and the strawberry flavour that are controlled to in-house specifications. Satisfactory certificates of analysis have been provided for all excipients. Excipients have been declared free of TSE risk.

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 presented in aluminium – aluminium / paper (peel) blister packs. The pack is a peel-to-open rigid strip formed from a laminate of aluminium foil and plastic films sealed to a paper-based laminate of aluminium foil.

The 4mg tablets will be presented in packs containing 2, 4, 6, 10, 20 and 30 tablets, with hospital packs of 10, 50, 10x6, 10x10 and 500 tablets. The 8mg tablets will be available in packs containing 2, 4, 6, 9, 10 and 30 tablets, with hospital packs of 10, 50, 10x6, 10x10 and 500 tablets.

It has been stated that the packaging components comply with Directive 90/128/EEC, as amended with respect to their suitability for contact with food.

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. The storage conditions are “Store in the original package”.

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

Bioequivalence

The applicant submitted a comparative pharmacokinetic study. The objective of this study was to evaluate the comparative bioavailability between Ondansetron Tablets 8 mg Flashtab (Teva Pharmaceutical industries Ltd., Israel), Zofran™ Melt 8mg (Glaxo Wellcome, UK Ltd) and Zofran™ tablets 8mg (Glaxo Wellcome, UK Ltd), in 24 healthy male subjects under fasting conditions. This study compared the rate and extent of absorption of Ondansetron 8 mg Orodispersible Tablets (test, Treatment A) versus Zofran® Melt 8 mg orodispersible tablets (reference 1, Treatment B) and Zofran® 8 mg tablets (reference 2, Treatment C), marketed in the UK

This was a blinded, single dose, randomized, 3-period, 6-sequence, 3-treatment, crossover study designed to evaluate the comparative bioavailability of three formulations of ondansetron. Subjects were randomly assigned to one of the six dosing sequences ABC, ACB, BAC, BCA, CAB, or CBA. Concentrations of ondansetron were measured from the plasma samples collected over a 24-hour interval after dosing in each period. Pharmacokinetic parameters: AUC_t , AUC_{inf} , C_{max} , T_{max} , K_{el} and $T_{1/2}$ were estimated based on ondansetron plasma levels for each subject that was assayed within each period of the study. Safety data were collected for each subject throughout the study by recording vital signs and reported adverse events.

Descriptive statistics for both test and reference products, were calculated for all pharmacokinetic parameters across all subjects analyzed. Analysis of Variance (ANOVA) was also carried out on the natural log-transformed AUC_t , AUC_{inf} , and C_{max} data and on the untransformed T_{max} , k_{el} and $T_{1/2}$ data. The following reported results are included: Geometric means of AUCs and C_{max} for both test and reference products. Ratios of geometric means of test versus reference products for AUCs and C_{max} . 90% confidence intervals of the above ratios.

The main pharmacokinetic findings are summarised in the tables below.

Treatment A vs. Treatment B Contrast (N =24)					
Parameter	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Arithmetic Means (CV%)				
	Treatment A	Treatment B			
AUC_{0-t} (ng*h/ml)	198.468 207.717 (28)	216.948 225.234 (27)	91.48	84.45 – 99.10	17
AUC_{inf} (ng*h/ml)	205.965 216.450 (29)	225.439 234.763 (28)	91.36	84.21 – 99.12	17
C_{max} (ng/ml)	27.116 27.646 (19)	30.244 31.158 (25)	89.66	81.68 – 98.42	19
T_{max}^a (h)	1.92 (43)	1.85 (44)	-	-	-
K_{el}^a (1/h)	0.1456 (15)	0.1453 (18)	-	-	-
$T_{1/2}^a$ (h)	4.86 (14)	4.91 (16)	-	-	-
Data Corrected for Measured Drug Content^b					
AUC_t (ng*h/ml)	195.728	212.903	91.93	84.87 – 99.59	-
AUC_{inf} (ng*h/ml)	203.121	221.236	91.81	84.62 – 99.61	-
C_{max} (ng/ml)	26.742	29.680	90.10	82.08 – 98.90	-

Treatment A vs. Treatment C Contrast (N= 24)					
Parameter	Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Arithmetic Means (CV%)				
	Treatment A	Treatment B			
AUC _{0-t} (ng*h/ml)	198.468 207.717 (28)	197.334 207.745 (32)	100.57	92.84 – 108.95	17
AUC _{inf} (ng*h/ml)	205.965 216.450 (29)	205.169 217.182 (34)	100.39	92.53 – 108.92	17
C _{max} (ng/ml)	27.116 27.646 (19)	26.874 27.496 (21)	100.90	91.92 – 110.76	19
T _{max} ^a (h)	1.92 (43)	2.04 (29)	-	-	-
K _{el} ^a (1/h)	0.1456 (15)	0.1461 (15)	-	-	-
T _{1/2} ^a (h)	4.86 (14)	4.86 (16)	-	-	-
Data Corrected for Measured Drug Content^b					
AUC _t (ng*h/ml)	195.728	198.525	98.59	91.01 – 106.80	-
AUC _{inf} (ng*h/ml)	203.121	206.407	98.41	90.70 – 106.77	-
C _{max} (ng/ml)	26.742	27.036	98.91	90.11 – 108.57	-

^a Presented as arithmetic mean (CV%) only.

^b Geometric means, ratio of geometric means, and confidence intervals are presented.

There were a total 8 adverse events involving 3 subjects in the study. These included constipation (2), headache (2), common cold (2), cough (1) and rhinorrhea (1). 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 the relative mean AUC_t 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, Teva Pharmaceutical Industries Ltd test drug of Ondansetron Tablets 8mg Flashtab, exhibited equivalent rate and extent of absorption to ZofranTM Melt 8mg and to ZofranTM tablets 8mg, in healthy volunteers, after a single oral-dose, under fasting conditions and therefore, they are bioequivalent drug products

Assessor's Comment

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

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

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.

The indications, dose and dose schedule are in line with those of the reference product.

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

Summary of Product Characteristics, Patient Information Leaflet and Labelling

Minor amendments were made to the Summary of Product Characteristics to bring it in line with the reference product's Summary of Product Characteristics. Subsequent minor changes to the Patient Information Leaflet and packaging were also made.

Assessor's Overall Conclusion

A Marketing Authorisation was granted.

Overall Conclusion and Risk/Benefit Analysis

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.

Pre-Clinical

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

Clinical

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.

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 is a generic medical product of Zofran. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 4 th May 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 18 th August 2004.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 15 th March 2005, 27 th June 2006 and 24 th April 2007 and on the medical assessment on 1 st October 2004
4	The applicant provided further information in regard to the quality assessment on 14 th February 2006, 30 th November 2006, 19 th March 2007 and 17 th May 2007 and on the medical assessment on 14 th February 2006.
5	The application was determined on 13 th August 2007.

Steps Taken after Assessment

Not applicable.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of ondansetron base.

Each tablet contains lactose and aspartame.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

White to off white, round, flat bevelled edge tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7301".

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.

4.2 Posology and method of administration

Place the tablet on top of the tongue, where it will disperse within seconds, then swallow.

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 as shown below.

Emetogenic chemotherapy and radiotherapy

Ondansetron can be given either by rectal, oral, 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 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 8 mg twice daily.

Highly emetogenic chemotherapy (e.g. 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 8 mg twice daily.

Children

Ondansetron may be administered as a single intravenous dose of 5 mg/m² 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 (as orodispersible tablets, tablets or syrup) 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 alterations 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 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 ondansetron 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 the active substance or to any of the excipients.

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.

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

Caution in patients with phenylketonuria.

Ondansetron Orodispersible Tablets contain lactose and should therefore not be used in patients with rare genetic disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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 substances commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic 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 the fetus, 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 or cause sedation.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Alimentary tract and metabolism – Antiemetics and antinauseants – Serotonin (5HT₃) antagonists.

ATC code A04A A01.

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 neurones 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 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 300 ml/min at 12 years of age to 100 ml/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 of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Basic butylated methacrylate copolymer (Eudragit E100)

Precipitated silica, hydrated

Strawberry flavour (maltodextrin, arabic gum, lactose, triethyl citrate)
Aspartame
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Aluminium – Aluminium / Paper (Peel) blisters containing 2, 4, 6, 10, 20 & 30 orodispersible tablets. Hospital packs of 10, 50, 10x6, 10x10 & 500 orodispersible tablets.

6.6 Special precautions for disposal

Do not attempt to push Ondansetron Orodispersible Tablets through the lidding foil.

Peel back the lidding foil of one blister and gently remove the tablet.

Place the tablet on top of the tongue, where it will disperse within seconds then swallow.

7 MARKETING AUTHORISATION HOLDER

Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0685

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/08/2007

10 DATE OF REVISION OF THE TEXT

13/08/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg of ondansetron base.

Each tablet contains lactose and aspartame.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

White to off white, round, flat bevelled edge tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "7302".

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.

4.2 Posology and method of administration

Place the tablet on top of the tongue, where it will disperse within seconds, then swallow.

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 as shown below.

Emetogenic chemotherapy and radiotherapy

Ondansetron can be given either by rectal, oral, 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 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 8 mg twice daily.

Highly emetogenic chemotherapy (e.g. 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 8 mg twice daily.

Children

Ondansetron may be administered as a single intravenous dose of 5 mg/m² 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 (as orodispersible tablets, tablets or syrup) 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 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 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 ondansetron 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 the active substance or to any of the excipients.

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.

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

Caution in patients with phenylketonuria.

Ondansetron Orodispersible Tablets contain lactose and should therefore not be used in patients with rare genetic disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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 substances commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic 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 the fetus, 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 or cause sedation.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism – Antiemetics and antinauseants – Serotonin (5HT₃) antagonists.

ATC code A04A A01.

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 neurones 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 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 300 ml/min at 12 years of age to 100 ml/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 of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Basic butylated methacrylate copolymer (Eudragit E100)
Precipitated silica, hydrated
Strawberry flavour (maltodextrin, arabic gum, lactose, triethyl citrate)
Aspartame
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Aluminium – Aluminium / Paper (Peel) blisters containing 2, 4, 6, 9, 10 & 30 orodispersible tablets. Hospital packs of 10, 50, 10x6, 10x10 & 500 orodispersible tablets.

6.6 Special precautions for disposal

Do not attempt to push Ondansetron Orodispersible Tablets through the lidding foil.
Peel back the lidding foil of one blister and gently remove the tablet.
Place the tablet on top of the tongue, where it will disperse within seconds then swallow.

7 MARKETING AUTHORISATION HOLDER

Teva UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG

England

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0686

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

13/08/2007

10 DATE OF REVISION OF THE TEXT

13/08/2007

Labels and Leaflet

PAGE 1: FRONT FACE (INSIDE OF REEL)



ONDANSETRON 4 & 8 mg ORODISPERSIBLE TABLETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

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

IN THIS LEAFLET:

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

The name of your medicine is Ondansetron 4 mg or 8 mg Orodispersible Tablets.

- The active ingredient is ondansetron base.
- Other ingredients are: mannitol, basic butylated methacrylate copolymer, hydrated precipitated silica, aspartame (E951), croscopolvidone, magnesium stearate and strawberry flavour (maltodextrin, arabic gum, lactose, triethyl citrate).
- The 4 mg orodispersible tablets are available in pack sizes* of 2, 4, 6, 10, 20 and 30 orodispersible tablets; hospital packs of 10, 50, 10x6, 10x10 and 500 orodispersible tablets.
- The 8 mg orodispersible tablets are available in pack sizes* of 2, 4, 6, 10, 20 and 30 orodispersible tablets; hospital packs of 10, 50, 10x6, 10x10 and 500 orodispersible tablets.

The Marketing Authorisation holder and company responsible for manufacture:
TEVA UK Limited, Eastbourne, BN22 9AG.

1 ONDANSETRON; WHAT IT IS AND WHAT IT'S USED FOR

- Each orodispersible tablet (for dissolving on the tongue) contains 4 mg or 8 mg of ondansetron. Ondansetron belongs to a group of medicines called anti-emetics, which prevent nausea and vomiting (feeling sick or being sick).
- Some medical and surgical procedures can make you feel sick (nausea) or be sick (vomit). Ondansetron tablets may stop these effects.

2 BEFORE YOU TAKE ONDANSETRON

Do not take Ondansetron if you:

- Are sensitive to any of the ingredients in your medicine.

Talk to your doctor if you have:

- Ever suffered an allergic reaction to other similar

- medicines, e.g. granisetron or tropisetron.
- Phenylketonuria (an inherited disorder where the enzyme responsible for conversion of phenylalanine into tyrosine is defective).
- A blockage in your gut or if you have severe constipation.

Tell your doctor if you are taking any of the following:

- medicines such as phenytoin or carbamazepine (mostly used in the treatment of epilepsy) or rifampicin (an antibiotic) as they may reduce the effect of Ondansetron.
- Tramadol (painkiller) as Ondansetron might reduce the effect.

Pregnancy and Breast-feeding:

- Do not take Ondansetron if you are pregnant, planning to become pregnant or breast-feeding.

Important information about some of the ingredients of your medicine:

- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
- Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

3 HOW TO TAKE ONDANSETRON

Your doctor has decided the dose which is suited to you. Always follow your doctor's instructions and those which are on the pharmacy label. If you do not understand these instructions, or you are in any doubt, ask your doctor or pharmacist.

These tablets are prescribed to:

- Prevent nausea (feeling sick) and vomiting (being sick), or
- Treat nausea and vomiting.

The usual dosage instructions are given below:

For patients receiving chemotherapy and/or radiotherapy that causes nausea and vomiting:

Adults (including the elderly):

The recommended dose is 8 mg 1 to 2 hours before chemotherapy or radiotherapy followed by 8 mg 12 hours later. After the first 24 hours following chemotherapy or radiotherapy, 8 mg twice a day for up to 5 days can be taken to prevent delayed or prolonged nausea or vomiting.

Children:

The usual dose is up to 4 mg twice a day, which may be given for up to 5 days following chemotherapy.

To prevent nausea and vomiting after an operation:

Adults (including the elderly):

A dose of 16 mg can be taken 1 hour before the operation. Alternatively, a dose of 8 mg can be taken 1 hour before the operation, followed by two further 8 mg doses at 8 hourly intervals.

Children (aged 2 years and over):
It is recommended that an intravenous injection containing Ondansetron should be given.

Patients with liver problems:
The total daily dose should not exceed 8 mg.

Take the tablets as follows:

- Do not push the tablet out of the pocket, as this will crush it
- Each strip contains tablets separated in pockets by perforations. Tear off one tablet pocket along the dotted lines (Figure 1)



Figure 1

- Carefully peel off the lidding foil, starting in the corner indicated by the arrow (Figures 2 and 3)



Figure 2



Figure 3

Keep your hands dry and take the tablet out of the strip.

- The tablet can be placed on the tongue, where it will quickly dissolve. These tablets can be taken with or without water.

If you take more Ondansetron than you should

If you (or someone else) swallow a lot of the tablets all together, or if you think a child has accidentally swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Overdose can cause temporary problems with your sight, severe constipation or feeling dizzy or faint.

If you forget to take Ondansetron

If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time.

Once you have started to take Ondansetron

Ondansetron should start to work within 1 to 2 hours of taking the dose. Continue to take your tablets as on the label, but do not take more than your doctor has recommended. If you continue to feel sick then you should tell your doctor.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Ondansetron can cause side effects, although not everybody gets them.

If you experience the following, stop taking Ondansetron and tell your doctor immediately or go to the casualty department at your nearest hospital:

- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat which may cause difficulty swallowing or breathing).

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

The following side effects have been reported at the approximate frequencies shown:

- Very common (affecting more than one person in 10):**
- Headache.

- Common (affecting fewer than one person in 10 but more than one person in 100):**
- Flushing or a feeling of warmth
 - Constipation.

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):

- Fits
- Abnormal muscle rigidity, abnormal muscular movements
- Abnormal eye movement, upward rolling of the eyes
- Hiccups
- Low blood pressure causing a light-headed feeling
- Chest pain, irregular heart rate, slowing of the heart rate
- Liver function tests may be affected by ondansetron.

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):

- Dizziness
- Temporary visual disturbances, e.g. blurred vision.

Very rare (affecting fewer than one person in 10,000):

- Temporary blindness, which usually resolves within 20 minutes.

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 pharmacist.

5 STORING ONDANSETRON

Keep Ondansetron out of the reach and sight of children. Do not transfer to another container. Store in the original package in order to protect from light. Do not use Ondansetron after the expiry date shown on the outer packaging. Return all unused medicines to your pharmacist for safe disposal.

Revised April 2007



TEVA UK Limited

84007-T



Text and Varnis area for Overpr batch number a

Each tablet contains 4 mg of ondansetron base. Also includes lactose and aspartame (E951).

DOSAGE:
Use as directed by the physician. Place tablet on the tongue, where it will melt within seconds, and then swallow. Please read the enclosed leaflet.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Store in the original package in order to protect from light.

Ondansetron 4 mg Orodispersible Tablets

Please affix dispensary label here

MA Holder:
TEVA UK Limited,
Easbourne, BN22 8AG.
PL 0289/0685
84004-T

UK Reg'd T.M. ©

Tear along the dotted lines

Carefully peel off the lidling foil...

...starting in the corner indicated by the arrow

5 017007 302094 >

Ondansetron
4 mg Orodispersible tablets
10 Tablets

Ondansetron

4 mg Orodispersible Tablets

For Oral Use

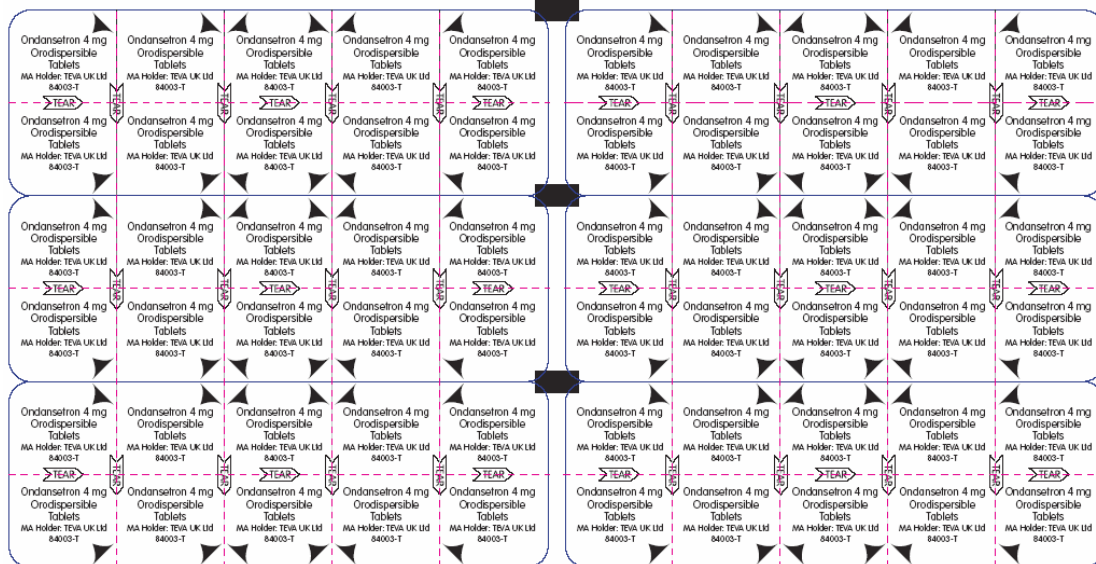
10 Tablets

1 2 3 4 5 6 7
8 9 10 11
12 13

Ondansetron 4 mg Orodispersible Tablets

10 Tablets

47 x 16
x 134mm



Foil Width is 258mm ± 0.5mm

