

**ONDANSETRON 4MG FILM-COATED TABLETS
PL 12762/0163**

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PL 12762/0164**

UKPAR

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LAY SUMMARY

The MHRA granted Goldshield Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg Film-Coated Tablets (PL 12762/0163) and Ondansetron 8mg Film-Coated Tablets (PL 12762/164). These are prescription-only medicines (POM) for the prevention of nausea or vomiting as a result of chemotherapy/radiotherapy or after an operation.

Ondansetron Film-Coated Tablets contain the active ingredient ondansetron, which is an antiemetic medicine.

The test product was considered the same as the reference products Zofran™ 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 Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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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 Film-Coated Tablets (PL 12762/0163) and Ondansetron 8mg Film-Coated Tablets (PL12762/0164) on 19th February 2007. The products are prescription-only medicines.

These are two strengths of Ondansetron Film-Coated Tablets, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, and have been shown to be generic medicinal products of the original, Zofran® 4mg and 8mg currently authorised to Glaxo Wellcome Limited following a change of ownership in December 1993. These products were originally authorised in March 1990 to Glaxo Operations UK Limited. The reference products have therefore been authorised in the EU for more than 10years.

The products contain the active ingredient ondansetron, a potent, highly selective serotonin (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. 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 Film-Coated 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 Zophren® 8mg (Glaxo-Wellcome, France). Consequently, all sections of this Scientific Discussion refer to both 4mg and 8mg products.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

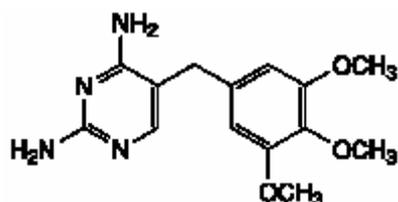
Ondansetron Hydrochloride

INN: Ondansetron Hydrochloride

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

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

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



Molecular formula: C₁₈H₁₉N₃O. HCL. 2H₂O

Molecular weight: 365.86

Physical form: White to off-white crystalline powder

Solubility: Sparingly soluble in water and alcohol, slightly soluble in dichloromethane, very slightly soluble in acetone, chloroform and in ethyl acetate.

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

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

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 double LDPE bags (transparent and black) in a small fibre board drum. The specifications and typical analytical test reports are provided and are satisfactory.

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

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

Appropriate stability data have been generated supporting a retest period of 24 months, when the active substance is stored in air tight containers and protected from light.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, purified water, magnesium stearate, maize starch, hypromellose, titanium dioxide (E171) and yellow iron oxide (E172).

Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of yellow iron oxide (E172) which complies with the 95/45/EC. Satisfactory certificates of analysis have been provided for all excipients. With the exception of magnesium stearate and lactose monohydrate, none of the excipients used contain material of animal or human origin. A satisfactory TSE certificate of suitability has been provided for the supplier of magnesium stearate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

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 blisters composed of aluminium and polyvinyl chloride (PVC). 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 presented in packs containing 15, 30 and 60 tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 25 degrees”.

Conclusion

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

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

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

Ondansetron is a potent highly selective 5HT₃ receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of post operative nausea and vomiting. These indications are consistent with those of the cross referenced product licences.

2. INDICATIONS

Proposed indication,

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

The proposed indications have been compared with the current versions of the Zofran SmPCs and are considered satisfactory. Consistent with the SmPC for Zofran 4 & 8mg tablets, PL 10949/0110/0111.

3. DOSE & DOSE SCHEDULE

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

4. TOXICOLOGY

Not assessed. None is required for an application for this type.

5. CLINICAL PHARMACOLOGY

Pharmacokinetics

A comparative clinical pharmacokinetic study has been submitted.

The study was conducted under the provisions of the appropriate Ethical and GCP guidelines.

A clinical pharmacology healthy volunteer study has been submitted to demonstrate bioequivalence.

This is considered appropriate and acceptable.

The study was an open two period single dose, randomised crossover study comparing the bioavailability of a single dose of two 8mg ondansetron film-coated tablets in healthy volunteer subjects.

The objective of the study was to determine whether the test product, ondansetron hydrochloride 8mg film coated tablets (Rivopharm SA, Switzerland) and the reference product, Zophren® 8mg film coated tablets (Glaxo Wellcome, France) were bioequivalent. For this purpose the rate and extent of absorption of ondansetron after administration of 8mg of each of the two formulations, were compared.

The reference product was Zophren, Ondansetron hydrochloride 8mg tablets, Glaxo Wellcome, France and the test product was the applicant's Ondansetron hydrochloride 8mg film coated tablets.

The test product was compared to the reference product with respect to the pharmacokinetic variables C_{max} , $C_{max}/AUC(0-\infty)$, $t_{1/2,z}$, $AUC(0-t_{last})$ and $AUC(0-\infty)$ using an analysis of variance with sequence, subject (sequence), product and period effects after logarithmic transformation of the data. Bioequivalence of the test product and the reference product was assessed on the basis of the confidence intervals for the variables ($AUC(0-\infty)$ and C_{max} , in relation to the conventional bioequivalence range of 80% to 125%.

RESULTS

Zophren® (Reference product)		
Variable	Geometric mean (SD)	Range
AUC(0-∞) (ng•h/ml)	324 (1.48)	150 - 647
C_{max} (ng/ml)	53.4 (1.30)	33.8 – 86.0

Ondansetron hydrochloride (Test product)		
VARIABLE	Geometric mean (SD)	Range
AUC(0-∞) (ng•h/ml)	324 (1.39)	154 – 737
C_{max} (ng/ml)	51.6 (1.30)	32.5 – 89.6

TEST VS REFERENCE

VARIABLE	Geometric mean (SD)	Range
AUC(0-∞) (ng•h/ml)	100	94.9 ; 105
C_{max} (ng/ml)	96.7	91.0 ; 103

It is considered that the bioequivalence demonstrated by the results obtained from the statistical analysis of the data is considered sufficient to demonstrate essential similarity or equivalence and allow inter changeability of the test and the reference products to be claimed.

6. EFFICACY

No original data submitted for assessment. Bioequivalence has been established. No new or unexpected clinical efficacy or safety concerns arise from the approval of these applications.

7. SAFETY

No original data submitted for assessment. Bioequivalence has been established. No new or unexpected clinical efficacy or safety concerns arise from the approval of these applications.

8. EXPERT REPORT

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

9. SUMMARY OF PRODUCT CHARACTERISTICS

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

10. PATIENT INFORMATION LEAFLET

This is satisfactory.

11. LABELLING

This is satisfactory.

12. CONCLUSIONS

The applicant appears to have demonstrated bioequivalence. No new or unexpected clinical safety concerns arise from these applications. Marketing authorisations should be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**QUALITY**

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

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Ondansetron 8mg Film-Coated Tablets and Zophren, Ondansetron hydrochloride 8mg tablets (Glaxo Wellcome, France). Given that linear kinetics apply between the 4mg and 8mg tablets, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 4mg tablets is not considered necessary.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT 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.

**ONDANSETRON 4MG FILM-COATED TABLETS
PL 12762/0163****ONDANSETRON 8MG FILM-COATED TABLETS
PL 12762/0164****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 15 th January 2003.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 6 th March 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 19 th June 2003 and further information relating to the quality dossiers on 19 th June 2003, 13 th July 2004, 12 th April 2005, 4 th January 2006, 26 th April 2006 and 26 th June 2006 .
4	The applicant responded to the MHRA's requests, providing further information on 8 th March 2004 for the clinical sections and again on 8 th March 2004, 21 st January 2005, 4 th January 2006, 20 th February 2006, 26 th June 2006 and 16 th August 2006 for the quality sections
5	The applications were determined on 19 th February 2007

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4mg, film-coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4mg tablet contains ondansetron hydrochloride dihydrate equivalent to 4mg of ondansetron.

Excipients: Lactose monohydrate. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Tablet - yellow to pale brown, oval, film-coated tablet engraved 'FW631' on one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

Ondansetron is indicated in children from the age of 2 years.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING.

Adults:

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

- Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration. The recommended dose for oral administration is 8mg twice daily, 8mg 1-2 hours before treatment, followed by 8mg 12 hours later. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.
- Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, Ondansetron can be given either by rectal, intravenous or intramuscular administration. The recommended dose for oral

administration is 8mg twice daily. 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.

Paediatric population (children aged 2 years and over):

Ondansetron may be administered as a single intravenous dose of 5mg/m² 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 can be administered orally or by intravenous or intramuscular injection.

For oral administration: 16mg 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.

Paediatric population (children aged 2 years and over):

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

Elderly

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

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 preparation.

Due to the presence of lactose monohydrate, patients with the rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, 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

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established.

For ondansetron no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post natal development.

Caution should be exercised when prescribing to pregnant women.

Lactation

Ondansetron is excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of Ondansetron are administered to breast-feeding women. 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

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 (ATC code) - A04A A 01.

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.

5.2 PHARMACOKINETIC PROPERTIES

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

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

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

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

Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple

enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

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

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

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

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

5.3 PRECLINICAL SAFETY DATA

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Maize starch
Magnesium stearate

Tablet coat

Hypromellose (E464)
Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs of 15, 30 or 60 tablets comprising PVC film and aluminium foil lidding.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited

NLA Tower

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

United Kingdom

Telephone: 0208 410 2159

Fax: 0208 686 0807

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0163

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2007

10 DATE OF REVISION OF THE TEXT

19/02/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8mg, film-coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 8mg tablet contains ondansetron hydrochloride dihydrate equivalent to 8mg of ondansetron.

Excipients: Lactose monohydrate. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Tablet - yellow to pale brown, oval, film-coated tablet engraved 'FW641' on one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

Ondansetron is indicated in children from the age of 2 years.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING.

Adults:

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

- Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration. The recommended dose for oral administration is 8mg twice daily, 8mg 1-2 hours before treatment, followed by 8mg 12 hours later. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.
- Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, Ondansetron can be given either by rectal,

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

Paediatric population (children aged 2 years and over):

Ondansetron may be administered as a single intravenous dose of 5mg/m² 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 can be administered orally or by intravenous or intramuscular injection.

For oral administration: 16mg 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.

Paediatric population (children aged 2 years and over):

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

Elderly

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

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 preparation.

Due to the presence of lactose monohydrate patients with the rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, 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

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established.

For ondansetron no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post natal development.

Caution should be exercised when prescribing to pregnant women.

Lactation

Ondansetron is excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of Ondansetron are administered to breast-feeding women. 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

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 (ATC code) - A04A A 01.

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

5.2 PHARMACOKINETIC PROPERTIES

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

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

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

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

Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

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

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

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

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

5.3 PRECLINICAL SAFETY DATA

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Lactose monohydrate

Microcrystalline cellulose

Maize starch

Magnesium stearate

Tablet coat

Hypromellose (E464)

Titanium dioxide (E171)
Yellow iron oxide (E172)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs of 15, 30 or 60 tablets comprising PVC film and aluminium foil lidding.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited

NLA Tower

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

United Kingdom

Telephone: 0208 410 2159

Fax: 0208 686 0807

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0164

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2007

10 DATE OF REVISION OF THE TEXT

19/02/2007

PATIENT INFORMATION LEAFLET



Patient Information Leaflet

ONDANSETRON 4mg & 8mg FILM-COATED TABLETS

Please read this leaflet carefully before you take these tablets. It briefly outlines the most important things you need to know. If you want to know more about this medicine, or you are not sure about anything, ask your doctor or your pharmacist.

IN THIS LEAFLET:

1. WHAT IS ONDANSETRON?
2. WHAT IS ONDANSETRON USED FOR?
3. BEFORE YOU TAKE ONDANSETRON TABLETS.
4. HOW TO TAKE ONDANSETRON TABLETS
5. SIDE EFFECTS
6. STORING ONDANSETRON TABLETS
7. FURTHER INFORMATION

1. WHAT IS ONDANSETRON?

The name of your tablet is:

Ondansetron 4mg film-coated Tablets

Ondansetron 8mg film-coated Tablets

Ondansetron 4mg tablet is a film coated, yellow-pale brown, oval tablet marked FW631.

Ondansetron 8mg tablet is a film coated, yellow-pale brown, oval tablet marked FW641.

Ondansetron tablets are available in two strengths containing either 4mg or 8mg of the active, ondansetron, as ondansetron hydrochloride dihydrate.

The other ingredients are lactose monohydrate, microcrystalline cellulose, maize starch, magnesium stearate, hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172).

Each pack contains 15, 30 or 60 tablets.

The Marketing Authorisation holder and company responsible for manufacture is

Goldshield Pharmaceuticals Ltd., NLA Tower,

12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, United Kingdom.

2. WHAT IS ONDANSETRON USED FOR?

Ondansetron belongs to a group of medicines called anti-emetics. Some medical and surgical treatments can make you feel sick or be sick (nausea and vomiting). These tablets may stop these effects. Ask your doctor or pharmacist if you need additional information.

3. BEFORE YOU TAKE ONDANSETRON TABLETS:

- Have you been told you are allergic to ondansetron, any of the other ingredients in the tablets listed above, or any similar medicines?
- Are you currently taking any of the following medication: carbamazepine, phenytoin, rifampicin or tramadol?
- Have you been told that you have a blockage in your gut or you suffer from severe constipation?
- Do you think you may be pregnant?
- Are you breast-feeding?
- Have you been told your liver is not working as well as it should do?
- Have you been told that you have an intolerance to some sugars (such as lactose)?

If the answer to any of these questions is yes:

- Did you tell your doctor at the last visit or an earlier visit?

If you did **not** tell your doctor then you should do so as soon as possible and **before** starting the medicine.

Your doctor will advise you about taking the medicine.

• Breast-feeding

Ondansetron may pass into the mother's milk. It is better therefore that mothers taking these tablets do **not** breast-feed.

4. HOW TO TAKE ONDANSETRON TABLETS:

Ondansetron tablets can be prescribed for two reasons:

- To prevent feelings of sickness (nausea) and sickness (vomiting), or
- To treat nausea and vomiting.

Always take ondansetron tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Swallow each tablet whole with a little water.

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

The recommended dose is 8 mg, 1 to 2 hours before chemotherapy followed by 8 mg 12 hours later. After the first 24 hours following chemotherapy, ondansetron tablets can be given to prevent nausea and vomiting. The usual adult dose is 8 mg twice a day, which can be given for up to 5 days. The usual dose for a child is up to 4 mg twice a day, which can be given for up to 5 days, following chemotherapy.

To prevent nausea and vomiting after an operation: The usual adult dose is 16 mg before the operation, or 8 mg before the operation followed by two further doses of

8mg at eight hourly intervals. For children aged 2 years and over it is recommended that ondansetron is given as an intravenous injection.

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

- Your doctor will tell you how long to take ondansetron tablets. Do not stop taking the tablets early.
- If you have the impression that the effect of ondansetron tablets is too strong or too weak, talk to your doctor or pharmacist.
- If you see another doctor or go into hospital, tell the doctor or hospital staff that you are taking ondansetron tablets.

What to do if you miss a dose:

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

Do not take double the dose if you miss a dose.

What to do if you take too many tablets:

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

After starting to take your tablets:

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

5. SIDE EFFECTS:

Along with the desirable effects, a medicine may cause unwanted effects. Most people taking this medicine find it causes no problems. A few people can be allergic to some medicines.

If any of the following rare side effects come on soon after taking these tablets, do not take any more tablets and tell your doctor immediately:

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

Other possible side effects are:

- Headache
- Feeling of warmth in the head or stomach
- Hiccups
- Light-headed feeling
- Flushes of the face
- Upset bowels – constipation

The following side effects are very rare but if you have them you should let your doctor know **immediately** and do not take any more tablets.

- Upward rolling of the eyes
- Abnormal muscular stiffness, body movements or shaking
- Fits

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

If you feel unwell or have any other unusual discomfort you don't understand, it is important to tell your doctor as soon as possible.

If you don't feel better:

If your sickness does not get better while taking ondansetron then tell your doctor.

6. STORING ONDANSETRON TABLETS:

Keep ondansetron tablets and all medicines out of the reach and sight of children.

Do not store above 25°C. Store in the original packaging. Do not use the tablets after the expiry/use before date on the blister pack or carton.

What to do with any unused tablets:

If your doctor stops your treatment, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist.

7. FURTHER INFORMATION:

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

REMEMBER:

THIS MEDICINE IS ONLY FOR YOU

Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if they have the same symptoms as you. This medicine could be harmful to them or interfere with other treatments. Your medicine has been prescribed by your doctor specifically for you.

This leaflet was updated: August 2006.

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product Name	Reference No.
Ondansetron 4mg film-coated tablet	12762/0163
Ondansetron 8mg film-coated tablet	12762/0164

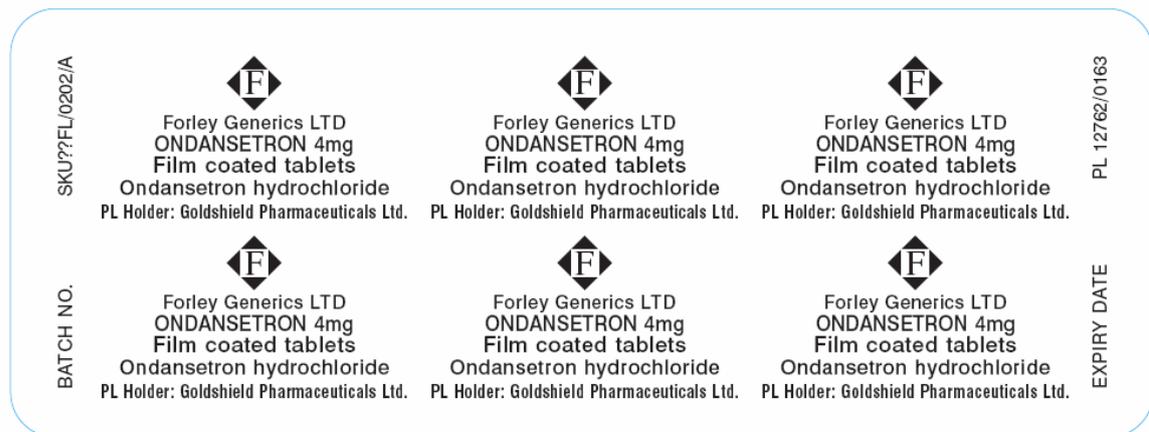
This is a service provided by the Royal National Institute of the Blind.

LABELLING

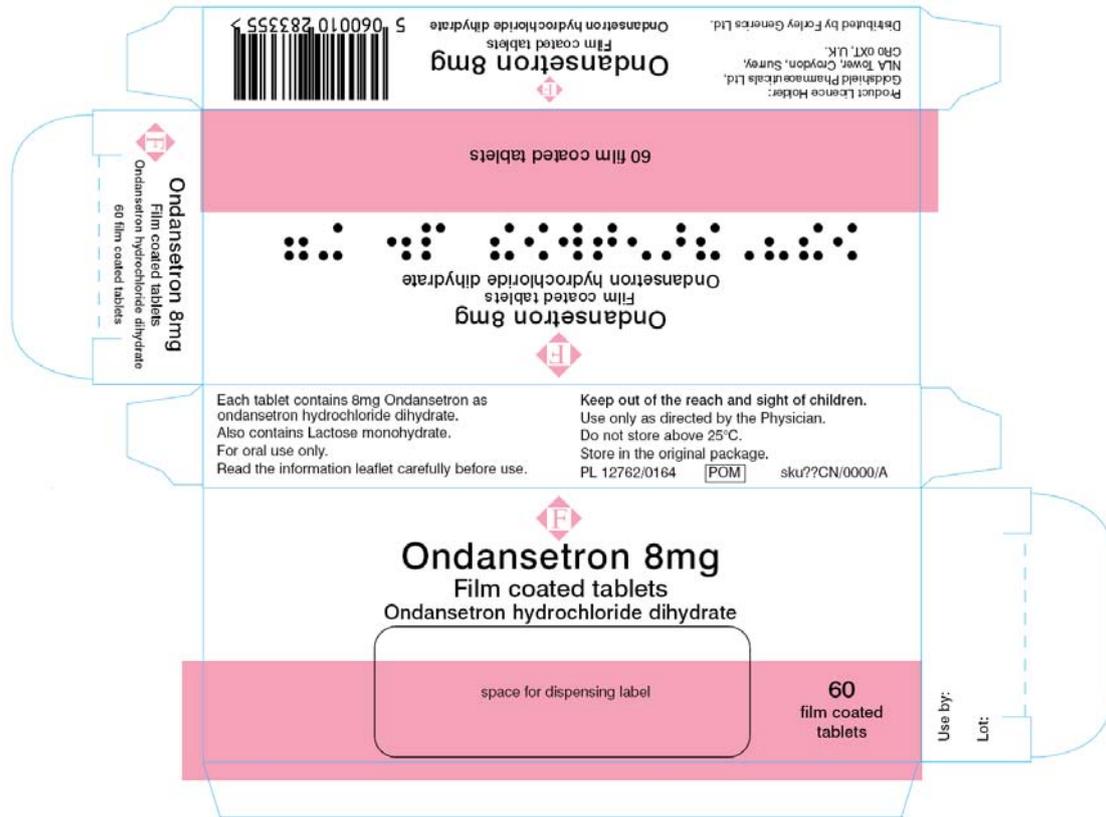
ONDANSETRON 4MG FILM-COATED TABLETS-CARTON



ONDANSETRON 4MG FILM-COATED TABLETS-BLISTER FOIL



ONDANSETRON 8MG FILM-COATED CARTON



ONDANSETRON 4MG FILM-COATED TABLETS-BLISTER FOIL

