ONDANSETRON 4 MG AND 8 MG TABLETS

PL 08137/0104

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UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Ondansetron 4 mg and 8 mg Tablets (Product Licence numbers: 08137/0104-5).

Some medical and surgical treatments and procedures can make you feel sick or actually be sick. Ondansetron belongs to a group of medicines known as anti-emetics, which may stop you feeling or being sick.

Ondansetron 4 mg and 8 mg Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

ONDANSETRON 4 MG AND 8 MG TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Ondansetron 4 mg and 8 mg Tablets to Neolab Limited on 14 March 2007. These medicines are only available by prescription.

These applications were submitted under the first paragraph of Article 10.1 of Directive 2001/83/EC, claiming to be generic versions of the original products, Zofran 4mg and 8mg Tablets (PL 10949/0110-0111). Zofran tablets are currently authorised in the UK to Glaxo Wellcome UK Limited, following a change of ownership in December 1993. These products were originally authorised on 7 March 1990 to Glaxo Operations UK Limited. The reference products have therefore been authorised in the EU for more than 10 years.

Ondansetron 4 mg and 8 mg Tablets are film-coated tablets containing, respectively, 4 and 8mg of the serotonin ($5HT_3$) antagonist ondansetron (as hydrochloride dihydrate). The products are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Ondansetron hydrochloride
Ph Eur name: Ondansetron hydrochloride dihydrate
USP name: Ondansetron hydrochloride

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

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

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

Structure

$C_{18}H_{19}N_30$. HCl. $2H_2O$ MW: 365.86

General Properties

Ondansetron hydrochloride dihydrate is a white to off-white crystalline powder sparingly soluble in water and alcohol, soluble in methanol, slightly soluble in dichloromethane, very slightly soluble in acetone, chloroform and in ethyl acetate. Solubility in water is 3.2% and 0.8% in 0.9% saline. The pH of an aqueous 1% w/v solution is approximately 4.6. The pKa is 7.4 such that free base precipitates when the pH is above the range 5.7-7. Ondansetron hydrochloride dihydrate is more stable in acidic media than at neutral pH. Ondansetron contains a single asymmetric carbon and is used as the racemate. There are no literature reports of polymorphism.

Ondansetron hydrochloride dihydrate is the subject of Ph Eur monograph. An appropriate specification in line with the Ph Eur monograph has been provided.

A satisfactory Certificate of Analysis has been provided for the current reference standard.

The drug substance is packed in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period. Ondansetron shows some sensitivity to temperature and moisture and should be protected from light.

DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, maize starch, magnesium stearate, purified water and opadry yellow Y-1-7000 white (containing: hydroxypropylmethylcellulose 2910, titanium dioxide E171, macrogol/PEG 400 and purified water).

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of opadry yellow Y-1-7000 white, which complies with in-house specifications. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

A copy of a TSE Certificate of Suitability has been provided for the magnesium stearate, which is of animal origin. A declaration has also been provided stating that another source of magnesium stearate of vegetable origin may be used.

It has been confirmed that milk used to manufacture the lactose monohydrate is sourced from healthy animals in the same conditions as milk collected for human consumption.

Satisfactory TSE declarations have been provided from the manufacturers of all other excipients used in manufacture of the products.

No genetically modified organisms are included in these products.

Manufacture
A description and flow-chart of the manufacturing method has been provided. The in-process controls and acceptance criteria are acceptable.

Process validation has been carried out on batches of each strength. All in-process results comply with the proposed acceptance criteria demonstrating the consistency of the manufacturing process. The process may be considered validated.

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 blister strips comprising PVC/PVdC/Aluminium foil enclosed in an outer carton. The tablets will be presented in packs containing 10, 30 or 100 tablets.

Satisfactory supplier and finished product manufacturer specifications and Certificates of Analysis have been provided for the packaging components. The materials are suitable for food use and comply with Directive 90/128/EEC (as

amended).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months with the storage precaution 'Store in the original package. Keep blister in the outer carton.' is appropriate.

Bioequivalence/bioavailability
Ondansetron is rapidly absorbed from the gastrointestinal tract and reaches maximum concentration in serum after approximately 1.6 hours. It is reported that there is some increase in bioavailability in the presence of food, although this is not thought to be clinically significant. There is a literature report (Clin. Pharmacokinet. 29 (2) 1995) to a non-proportional increase in systemic availability with 8, 16, 32 and 64 mg of ondansetron that may be the result of saturation of the first-pass metabolism.

Comparative *in vitro* dissolution profiles have been generated for Ondansetron 8mg Tablets and the UK reference product Zofran 8mg Film-coated Tablets, and for 4 mg tablets from both manufacturers. Testing was performed as for routine batch release. Both test and reference products studied in the bioequivalence study showed similar release profiles in pH 1.2 buffer, with all tablets releasing more than 90% ondansetron in 15 minutes, and an average of more than 99% released in 15 minutes.

Results (geometric means) from a two-way open randomised single-dose crossover study between the test and reference products, dosed fasted at a dose of 8mg. Ln transformed; ANOVA; n=24 male subjects. Washout period 7 days between phases. t=24 hours

Test parameter	Test product	Reference product	Point estimate (%)	90% confidence intervals (%)
AUC_{0-t} (ng h/ml)	292.23	281.93	103.65	96.48-110.41
$AUC_{0-\infty}$ (ng h/ml)	300.22	290.72	103.27	96.13-109.98
C_{max} (ng/ml)	54.29	56.40	96.25	91.85-101.07
t_{max} (h) *	1.79	1.74	-	-

* non-parametric analysis (Wilcoxon-Mann-Whitney)

As the 90% confidence intervals for the mean AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} values (following log transformation) are within 80-125%, the test and reference products may be considered bioequivalent, dosed under fasting conditions.

The applicant has provided a justification for not performing a study with the 4mg tablets. A biowaiver is accepted given that linear kinetics apply between 4mg and 8mg.

Plasma concentrations of ondansetron were determined using a validated method.

Product literature
The Summaries of Product Characteristics, Patient Information Leaflets and Labelling for these products are satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusions
Marketing authorisations may be granted for these products.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

Indications
The proposed indication is

"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."

This is considered satisfactory and to be fully consistent with the indications for Zofran 4 and 8mg tablets (PL 10949/0110-11).

Dose and dose schedule
The proposed dose and dosage schedules for these products have been compared with those in the Summary of Product Characteristics for Zofran in the UK.

The proposed schedules are considered satisfactory because they are fully consistent with the SPC for Zofran 4 and 8mg tablets.

Clinical pharmacology

Pharmacokinetics
A comparative bioavailability study has been submitted.
This was an open, single centre, two period, single dose, crossover study comparing a single dose of two 8 mg ondansetron tablet formulations with Zofran 8 mg tablets (Glaxo Welcome UK) in 24 healthy male volunteer subjects.

Results
Statistical methods: ANOVA, 90% confidence interval for the ratio of the population means for untransformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} were performed. T_{max} was evaluated by non-parametric Wilcoxon-Mann-Whitney two one-sided test procedure.

The 90% confidence interval of the relative C_{max} and AUC of the test to the reference Zofran product were within the 80-125% range.

Parameters	**Least square mean ± SD**		**Ratio (T/R)**
	Test (T)	**Reference (R)**	
C_{max} (ng/ml)	54.62 ± 6.29	56.62 ± 5.11	96.46
AUC_{0-t} (h.ng/ml)	297.71 ± 59.37	287.79 ± 60.21	103.45
AUC_{0-inf} (h.ng/ml)	305.65 ± 59.67	296.59 ± 61.01	103.05
T_{max} (h)	1.80 ± 0.19	1.75 ± 0.16	
K_{el} (1/h)	0.168 ± 0.021	0.166 ± 0.028	
$T_{½}$ (h)	4.19 ± 0.58	4.29 ± 0.68	

The 90% confidence intervals of ln-transformed parameters are summarised below:

Parameters	**Geometric mean**	**T/R**	**90% Confidence Interval**

	Test (T)	Reference (R)		for In-transformed data
C_{max} (ng/ml)	54.29	56.40	96.25	91.85 – 101.07%
AUC_{0-t} (h.ng/ml)	292.23	281.93	103.65	96.48 – 110.41%
AUC_{0-inf} (h.ng/ml)	300.22	290.72	103.27	96.13 – 109.98%

The bioequivalence demonstrated by the results obtained from the statistical analysis of the data is considered sufficient to demonstrate that the proposed products are generic to the reference product.

No new or unexpected safety concerns were reported in this study.

Efficacy
No original efficacy data on the formulation proposed for marketing were submitted for assessment, this is satisfactory.

Safety
No original safety data on the formulation proposed for marketing were submitted for assessment, this is satisfactory.

Summary of Product Characteristics
The text for sections 4 and 5 of the proposed SPCs is considered satisfactory and consistent with the SPCs for Zofran 4 and 8 mg tablets.

Patient information leaflet
The PIL is considered satisfactory. The PIL is consistent with the PILs for Zofran 4 and 8mg tablets.

Labelling
The proposed labelling is considered satisfactory.

Conclusions
Marketing Authorisations may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 4 mg and 8 mg 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

The efficacy of ondansetron is well established.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Ondansetron 4 mg and 8 mg Tablets. The risk benefit is therefore considered to be positive.

ONDANSETRON 4 MG AND 8 MG TABLETS

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 28 March 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 29 April 2003
3	Following assessment of the application the MHRA requested further information relating to the quality and clinical dossiers on 7 July 2003
4	The applicant responded to the MHRA's requests, providing further information on the quality and clinical dossiers on 4 September 2003, with an additional information on the quality dossier being given on 10 September 2003
5	Following assessment of the response the MHRA requested further information relating to the quality dossier on 8 January 2004
6	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 12 January 2004
7	Following assessment of the response the MHRA requested further information relating to the quality and clinical dossiers on 13 July 2004
8	The applicant responded to the MHRA's requests, providing further information on the quality and clinical dossiers on 21 August 2006
9	The application was determined on 14 March 2007

SUMMARY OF PRODUCT CHARACTERISTICS

PL 08137/0104:

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ondansetron 4 mg (as the hydrochloride dihydrate).

Excipient: Lactose monohydrate.

Full a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

Ondansetron 4 mg Tablets are white, round film-coated tablets marked “OSN 4” on one side and “NEO”on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Chemotherapy and radiotherapy induced nausea and vomiting

Adults:

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

Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration, using either Ondansetron 4 mg and 8 mg Tablets or other commercially-available ondansetron presentations.

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

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

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

Highly Emetogenic Chemotherapy (e.g., high-dose cisplatin): Ondansetron can be given either by rectal, intravenous or intramuscular administration, using other commercially-available ondansetron presentations.

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

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

Children:

Ondansetron may be administered as a single intravenous dose of 5mg/m^2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 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.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

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

Post-operative nausea and vomiting (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, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

For the treatment of established PONV: Intravenous or intramuscular administration is recommended.

Children (aged 2 years and over):

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

Elderly:

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

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

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

Patients with poor sparteine/debrisoquine metabolism:

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

4.3. Contraindications

Hypersensitivity to any component of the preparation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4. Special warnings and precautions for use

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

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

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

4.5. Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

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

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

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

4.6. Pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7. Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8. Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

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

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

Eye disorders

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

Very rare: Transient blindness predominantly during intravenous administration.

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

Cardiac disorders

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

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

Gastrointestinal disorders

Common: Constipation.

Hepatobiliary disorders

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

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

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Ondansetron does not alter plasma prolactin concentrations.

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 (15-32h) 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
Titanium dioxide E171
Macrogol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage
Store in the original package. Keep blister in the outer carton.

6.5. Nature and contents of container
Blister strips comprising PVC/PVdC/Aluminium foil enclosed in an outer carton. Pack sizes of 10, 30 or 100 tablets (not all packs may be marketed).

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Neolab Limited,
57 High Street,
Odiham, Hants
RG29 1LF,
UK

8. MARKETING AUTHORISATION NUMBER
PL 08137/0104

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/03/2007

10 DATE OF REVISION OF THE TEXT
14/03/2007

PL 08137/0105:

1. NAME OF THE MEDICINAL PRODUCT
Ondansetron 8 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains ondansetron 8 mg (as the hydrochloride dihydrate).

Excipient: Lactose monohydrate.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

Ondansetron 8 mg Tablets are white, round film-coated tablets marked “OSN 8” and “NEO” with a breakline on one side, plain on the other. The breakline is only to facilitate breaking if necessary for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Chemotherapy and radiotherapy induced nausea and vomiting

Adults:

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

Emetogenic Chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration, using either Ondansetron 4 mg and 8 mg Tablets or other commercially-available ondansetron presentations.

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

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

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

Highly Emetogenic Chemotherapy (e.g., high-dose cisplatin): Ondansetron can be given either by rectal, intravenous or intramuscular administration, using other commercially-available ondansetron presentations.

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

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

Children:

Ondansetron may be administered as a single intravenous dose of 5mg/m^2 immediately before chemotherapy, followed by 4mg orally twelve hours later. 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.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

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

Post-operative nausea and vomiting (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, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

For the treatment of established PONV: Intravenous or intramuscular administration is recommended.

Children (aged 2 years and over):

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

Elderly:

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

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

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

Patients with poor sparteine/debrisoquine metabolism:

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

4.3. Contraindications

Hypersensitivity to any component of the preparation.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4. Special warnings and precautions for use

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

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

4.5. Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol and propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally

compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

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

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

4.6. Pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7. Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8. Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

<u>Immune system disorders</u>

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

<u>Nervous system disorders</u>

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

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 (15-32h) 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
Titanium dioxide E171
Macrogol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store in the original package. Keep blister in the outer carton.

6.5. Nature and contents of container

Blister strips comprising PVC/PVdC/Aluminium foil enclosed in an outer carton. Pack sizes of 10, 30 or 100 tablets (not all packs may be marketed).

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Neolab Limited,
57 High Street,
Odiham,
Hants
RG29 1LF,

UK

8. MARKETING AUTHORISATION NUMBER
PL 08137/0105

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/03/2007

10 DATE OF REVISION OF THE TEXT
14/03/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET
Ondansetron 4 mg & 8 mg Tablets

Ondansetron hydrochloride dihydrate

What you should know about Ondansetron Tablets

Please read this leaflet carefully before you start to take your medicine. The leaflet provides a summary of the information available on your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

What is in your medicine?

Each tablet contains 4 mg or 8 mg of the active ingredient, ondansetron (as ondansetron hydrochloride dihydrate). Other ingredients include: lactose monohydrate, microcrystalline cellulose, maize starch, magnesium stearate, hypromellose, titanium dioxide (E171) and macrogol.

Ondansetron 4 mg Tablets are white, round film-coated tablets marked 'OSN 4' on one side and 'NEO' on the other.
Ondansetron 8 mg Tablets are white, round film-coated tablets marked 'OSN 8' and 'NEO' with a breakline on one side and plain on the other.

The tablets are available in packs containing 30 x 4 mg tablets or 10 x 8 mg tablets.

The Marketing Authorisation Holder and manufacturer responsible for release of the tablets is Neolab Limited, 57 High Street, Odiham, Hants, RG29 1LF.

What is Ondansetron?

The active ingredient in your tablets, ondansetron, belongs to a group of medicines known as anti-emetics. Some medical and surgical treatments and procedures can make you feel sick (this feeling is known as nausea) or actually be sick (known as vomiting). These medicines, including Ondansetron Tablets, may stop the nausea and vomiting.

Before taking your medicine

- Have you been told you are allergic to ondansetron, or to any of the other ingredients in the tablets (listed above), or to any similar medicines?
- Have you been told that you have an intolerance to some sugars? These tablets contain lactose.
- Do you suffer from severe constipation, or have you been told you have a blockage in your gut?
- Do you think you may be pregnant?
- Are you breast-feeding ?
- Have you been told you suffer from any liver problems?
- Do you suffer from epilepsy and take the medicine phenytoin or carbamazepine?
- Are you taking medicines called rifampicin (for the treatment of tuberculosis) or tramadol (for the relief of pain)?
- Do you have a problem with your heart?

If the answer to any of these questions is YES, then you should tell your doctor as soon as possible BEFORE starting the medicine (unless you have already told your doctor before). Your doctor will advise you about taking these tablets.

Breast-feeding
The ondansetron in these tablets may pass into breast milk. Mothers taking Ondansetron Tablets should not therefore breast-feed.

Driving and using machines
Ondansetron can cause visual disturbances and dizziness. If you are affected do not drive or operate machinery.

Taking your medicine

Take your Ondansetron Tablets as prescribed by your doctor and as stated on the carton label. The tablets should be swallowed whole with a little water.

The tablets should start to work within 1–2 hours. If you vomit the first dose back within 1 hour then repeat this dose. Otherwise take the tablets exactly as it says on the label. If you continue to feel sick, talk to your doctor.

Ondansetron Tablets can be prescribed either to prevent or to treat nausea and vomiting.

For nausea and vomiting caused by chemotherapy and / or radiotherapy:
The recommended adult dose is 8 mg 1-2 hours before chemotherapy, followed by 8 mg 12 hours later. After the first 24 hours following chemotherapy, Ondansetron tablets may be given to prevent nausea and vomiting. The usual dose for adults is 8 mg twice daily, which can be given for up to 5 days.

In children, the usual dose is up to 4 mg twice daily. This can be given for up to 5 days following chemotherapy. If Ondansetron Tablets have been prescribed for a child, make sure the tablets are given exactly as stated on the label.

XXXXX

Please read the back of this leaflet.

For prevention of nausea and vomiting after an operation:
The usual adult dose is 16 mg before the operation, or 8 mg before the operation plus two further doses of 8 mg at 8-hour intervals.

It is recommended that children aged 2 years and older be given ondansetron by intravenous injection. (Ondansetron-containing injections and suppositories are available, if your doctor wishes to prescribe these for you instead of Ondansetron tablets).

Patients with moderate to severe liver disease:
The total dose should not be more than 8 mg per day.

If you forget to take your medicine:
If you miss a dose, do not worry. Take a dose as soon as possible if you feel sick or vomit, or just take the next dose as normal.

If you take too many tablets:
It is important to take these tablets as directed – taking more than prescribed can make you ill. If you do take more than you should, tell your doctor or go to the nearest hospital casualty department AS SOON AS POSSIBLE. If you go to the hospital/doctor remember to take this leaflet and any remaining tablets with you so the doctor knows what you have taken.

Possible side effects

Most people have no problems when taking these tablets. Like all medicines, however, Ondansetron Tablets can cause unwanted side effects in some people.

Rarely, a few patients experience allergic reactions to some medicines. An allergic reaction may include some of the following rare side effects:
- swelling of the face, eyelids or lips
- sudden chest tightness or difficulty in breathing
- skin rash – red spots or hives (lumps)
- collapse

If you suffer from any of these unwanted side effects soon after first taking Ondansetron Tablets, stop taking the tablets and contact your doctor IMMEDIATELY.

Also tell your doctor IMMEDIATELY if you have any of the following side effects, which are uncommon:
- Rolling of your eyes
- Unusual muscle stiffness, uncontrolled body movements or shaking
- Fits

Patients may rarely experience blurring of vision and very rarely suffer from temporary blindness, which usually resolves within 20 minutes.

Other possible side effects include:
- Headache
- A feeling of warmth in the head or stomach
- Hiccups
- Light-headedness or dizziness
- Chest pain
- Slow or irregular heartbeat
- Flushing (reddening) of the face
- Stomach upset (constipation)

If you develop any of these side effects, continue to take the medicine but tell your doctor on your next visit.

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

If you feel unwell or you continue to feel sick, or you have any other side effects not mentioned in this leaflet, it is important to tell your doctor as soon as possible.

Storing your medicine

Do not keep this medicine after the expiry date shown on the carton. Return any leftover tablets to your pharmacist unless your doctor tells you to keep them.

Store the tablets in the original package. Keep the blister in the outer carton.

Keep all medicines out of the reach and sight of children. Your medicine can harm them.

These tablets have been prescribed for you. Only a doctor can prescribe these tablets for you. Do not give them to other people even if their symptoms are the same as yours. It may harm them.

This leaflet was prepared February 2007.

This leaflet applies to Ondansetron 4 mg and 8 mg Tablets only.

neolab

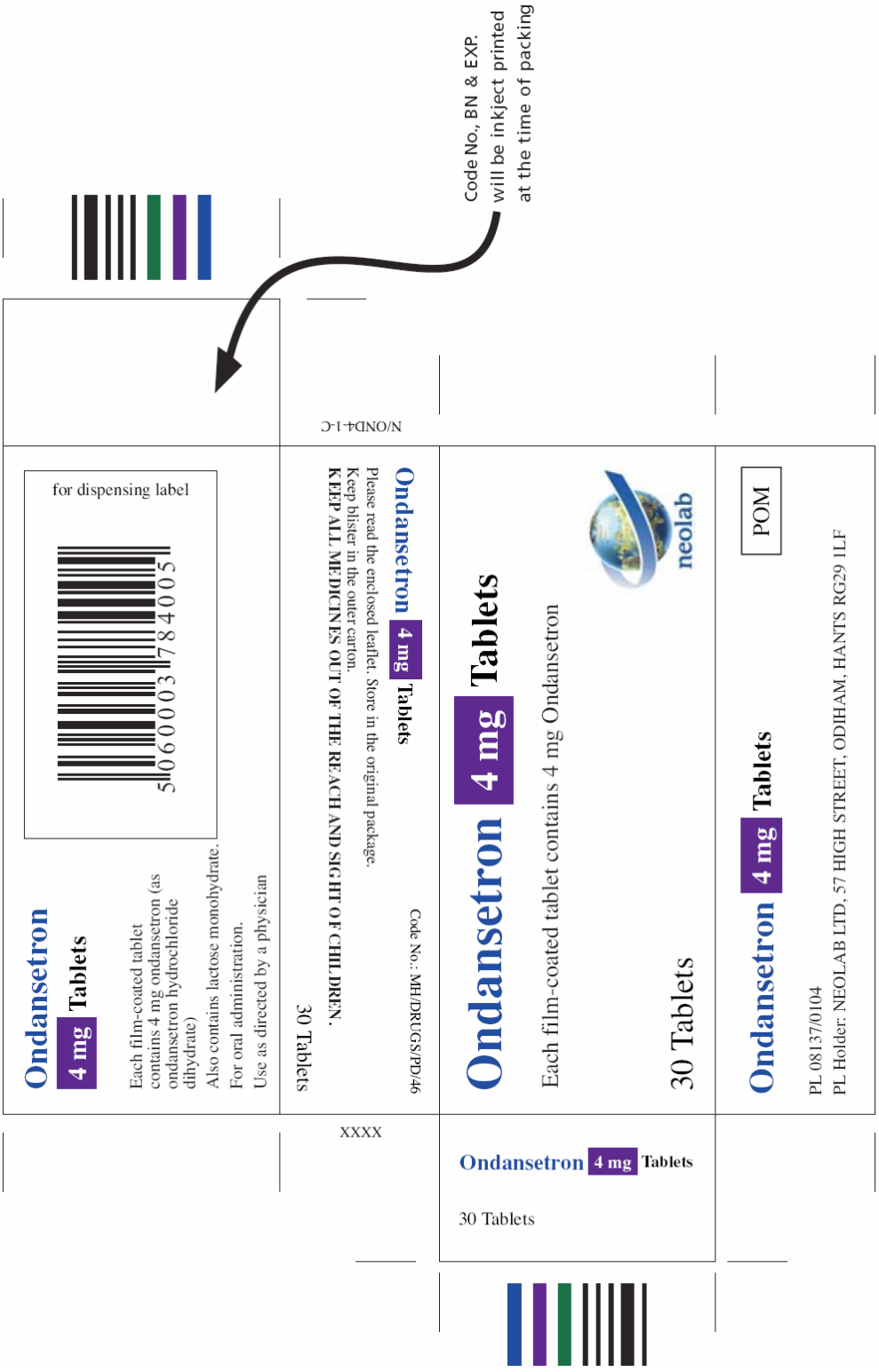
XXXXX

PACKAGING

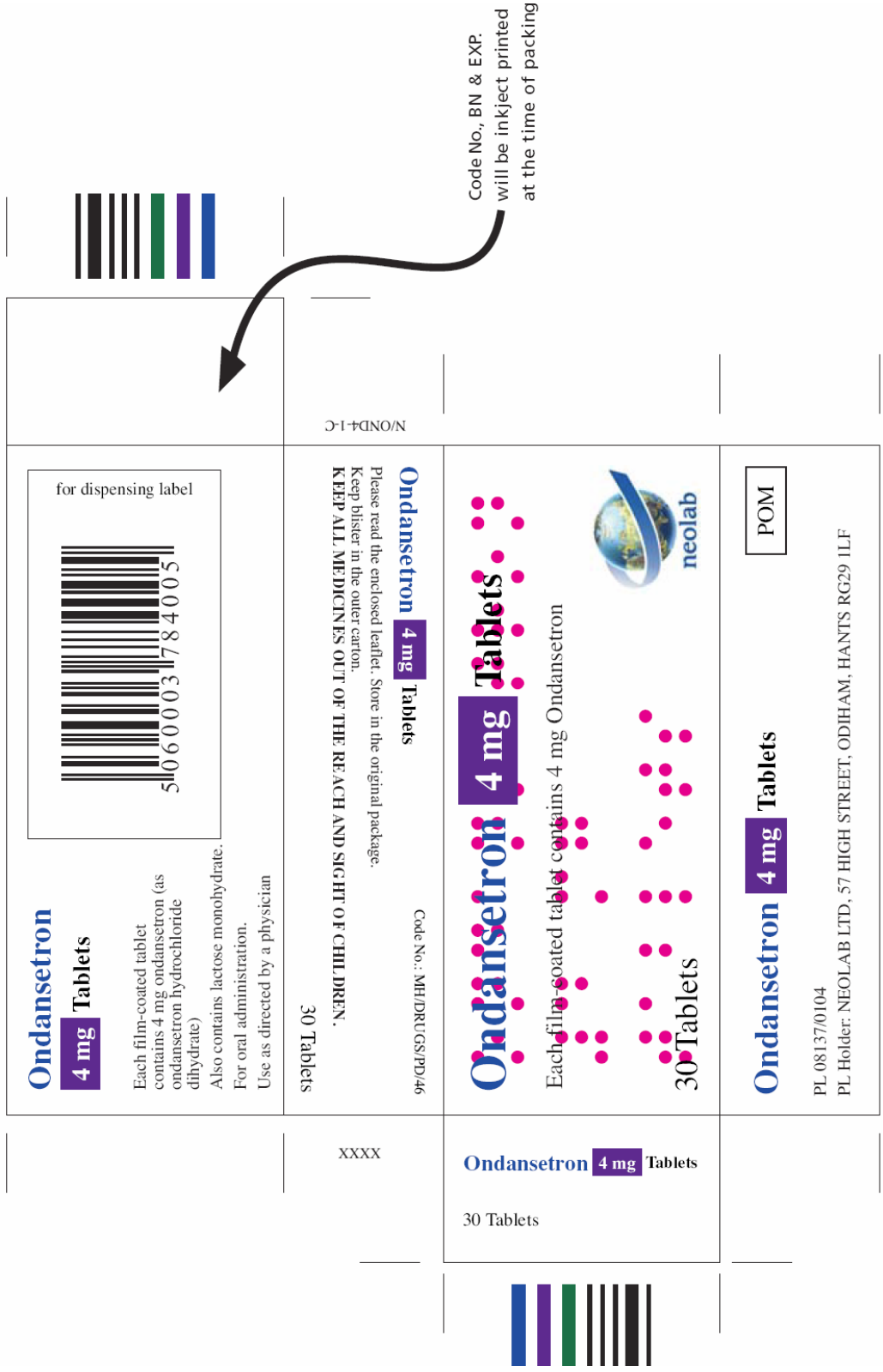
PL 08137/0104

Blister:

Carton:


Code No., BN & EXP.
will be inkject printed
at the time of packing
for dispensing label
5060003784005
Ondansetron
4 mg Tablets
Each film-coated tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate)
Also contains lactose monohydrate.
For oral administration.
Use as directed by a physician
N/ONDA-1-C
Ondansetron 4 mg Tablets
30 Tablets
KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.
Please read the enclosed leaflet. Store in the original package.
Keep blister in the outer carton.
Code No.: MH/DRUGS/PD/46
XXXX
Ondansetron 4 mg Tablets
Each film-coated tablet contains 4 mg Ondansetron
30 Tablets
neolab
Ondansetron 4 mg Tablets
30 Tablets
POM
Ondansetron 4 mg Tablets
PL 08137/0104
PL Holder: NEOLAB LTD, 57 HIGH STREET, ODIHAM, HANTS RG29 1LF

Carton with Braille:



PL 08137/0105

Blister:

Carton:


Code No., BN & EXP.
will be inkject printed
at the time of packing
N/ONDS-1-C
for dispensing label
5060003784012
Ondansetron
8 mg Tablets
Each film-coated tablet contains 8 mg ondansetron (as ondansetron hydrochloride dihydrate)
Also contains lactose monohydrate.
For oral administration.
Use as directed by a physician.
Ondansetron 8 mg Tablets
Please read the enclosed leaflet. Store in the original package.
Keep blister in the outer carton.
KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.
10 Tablets
Code No.: MH/DRUGS/PD/46
XXXX
Ondansetron 8 mg Tablets
Each film-coated tablet contains 8 mg Ondansetron
neolab
10 Tablets
Ondansetron 8 mg Tablets
10 Tablets
POM
Ondansetron 8 mg Tablets
PL 08137/0105
PL Holder: NEOLAB LTD, 57 HIGH STREET, ODIHAM, HANTS RG29 1LF

Carton with Braille: