ONDANSETRON 4MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0510

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LAY SUMMARY

The MHRA granted CP Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg Tablets (PL 04543/0508) and Ondansetron 8mg Tablets (PL 04543/0510) on 21st March 2006. These prescription only medicines (POM) are used for the management of nausea and vomiting caused by cancer chemotherapy and radiotherapy, and for the prevention of post-operative nausea and vomiting in adults and children.

Ondansetron Tablets contain the active ingredient ondansetron hydrochloride, which is an anti-emetic, used to prevent nausea and vomiting.

The data presented to the MHRA, pre licensing, demonstrated that Ondansetron 4mg and 8mg Tablets are equivalent to the approved products, Zofran 4mg and 8mg Tablets. Ondansetron Tablets can therefore be used interchangeably with Zofran Tablets.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Ondansetron Tablets outweigh the risks. Hence Marketing Authorisations have been granted.

ONDANSETRON 4MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0510

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 Tablets (PL 04543/0509) and Ondansetron 8mg Tablets (PL 04543/0510) to CP Pharmaceuticals Limited on 21st March 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to the original products Zofran 4mg and 8mg Tablets.

The products contain the active ingredient ondansetron hydrochloride and 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 in adults and children.

Ondansetron hydrochloride, a carbazole, is a selective inhibitor of type 3 serotonin (5-hydroxytryptamine) receptors ($5\text{-}HT_3$) that exhibits anti-emetic activity.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

These are abridged applications for Marketing Authorisation in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83 (as amended), first paragraph so called generic application.

The original products, Zofran 4mg Tablets, PL 00004/0376 and Zofran 8mg Tablets PL 00004/0377, were licensed in the UK on the 7th March 1990, to Glaxo. The licences have undergone a change of ownership due to the mergers of GlaxoSmithKline, current licences are PL 10949/0110 (4mg) and PL 10949/0111 (8mg).

The medicinal product used in the clinical studies is Zofron 8mg Tablets sourced from Greece.

2. COMMON TECHNICAL DOCUMENT SUMMARIES

2.1 INTRODUCTION
2.2 QUALITY OVERALL SUMMARY (QOS)

A satisfactory introduction and Quality Overall Summary have been provided.

3. DRUG SUBSTANCE

3.1 GENERAL INFORMATION

3.1.1 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

3.1.2 Structure

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

3.1.3 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 a 1% w/v solution in water is about 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, although Module 3 refers to a pseudo polymorph that melts at approximately 213°C.

3.2 MANUFACTURE

3.2.1 Manufacturing process description and process controls

A letter of access dated 20th July 2004 and the open part of Drug Master File (DMF) have been provided for the above source. The Applicant's part is identical to the version registered with the MHRA. No products have been authorised in the UK using this source of active substance.

The synthetic route has been provided.

3.2.2 Control of materials

No materials of animal or human origin are used in manufacture of the drug substance.

3.3 CHARACTERISATION

3.3.1 Impurities

Impurities A-H are described in the Ph Eur monograph.

Impurity A: (3RS)-3-[(dimethylamino)methyl]-9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one
Impurity B: 6,6′-methylenebis-[(3RS)- 9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one]
Impurity C: 9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one
Impurity D: 9-methyl-3-methylene-1,2,3,9-tetrahydro-4H-carbazol-4-one
Impurity E: 1H-imidazole
Impurity F: 2-methyl-1H-imidazole
Impurity G: (3RS)-3-[(1H-imidazol-1-yl)methyl(-9-methyl-1,2,3,9-tetrahydro-4H-carbazol-4-one

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

Four of the above impurities (ondansetron impurities A-D) are also described in the USP monograph for ondansetron hydrochloride.

3.4 CONTROL OF DRUG SUBSTANCE

3.4.1 Specification

Ondansetron hydrochloride dihydrate is the subject of Ph Eur monograph 01/2003:2016 corrected. The substance is also described in the USP/NF. Batches of drug substance are controlled to the specifications provided. The specifications provided satisfy the requirements of the Ph Eur monograph.

The proposed limits for residual solvents comply with ICH recommended limits.

3.4.2 Analytical procedures / validation

The active substance manufacturer uses the methods described in the Ph Eur monograph except the methods used for determining water and heavy metals. The active substance manufacturer has described alternative details for the preparation of reference standards for the related substances methods that will be used until the CRS reference standards for system suitability are available. A validated in-house method has been described for determination of residual solvents. The method for DSC analysis has been described. The methods are satisfactory.

The manufacturer of the finished product uses the methods described in the Ph Eur monograph.

3.4.3 Batch analyses

Satisfactory Certificates of Analysis have been provided. Data from the active substance manufacturer have been provided on 5 batches whilst data on 4 batches have been provided by the finished product manufacturer.

3.4.4 Justification of specification

The applicant has provided a justification for the proposed specification. Impurity B is considered qualified at a level of 0.4% on the basis of inclusion in the USP and Ph Eur monographs. On the basis of the transparency statement in the Ph Eur monograph, impurities A, C and E-H are considered qualified at a level of 0.2%.

3.5 REFERENCE STANDARDS OR MATERIALS

Satisfactory Certificates of Analysis have been provided for the current working standard of ondansetron hydrochloride dihydrate. The reference standards are provided by the active substance manufacturer.

3.6 CONTAINER CLOSURE SYSTEM

The drug substance is packed in sealed translucent polyethylene bags in HDPE drums. The bags are stated as complying with Ph Eur requirements. Satisfactory specifications and batch documentation have been provided for the above packaging components.

3.7 STABILITY

3.7.1 Stability summary and conclusions

Ondansetron shows some sensitivity to temperature and moisture and should be protected from light.

3.7.2 Post-approval stability protocol and stability commitment

A commitment has been provided in the DMF that the existing long term studies will be continued and that an annual batch will be added to the programme.

4. DRUG PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Table 1: Qualitative composition and function of ingredients

Ingredient	Function	Reference Standard
Core:		
Ondansetron hydrochloride * (equivalent to ondansetron)	Active ingredient	Ph Eur
Lactose monohydrate	Diluent	Ph Eur
Microcrystalline cellulose	Binder	Ph Eur
Pregelatinised starch	Disintegrant	Ph Eur
Magnesium stearate	Lubricant	Ph Eur
Film-coating (Opadry 20J22730 Yellow):		HSE
Hypromellose	Coating agent – binder	Ph Eur
Titanium dioxide	Opacifier	Ph Eur
Hydroxypropyl cellulose	Coating agent – binder	Ph Eur
Propylene glycol	Solubilizer	Ph Eur
Sorbitan Monooleate	Non-ionic surfactant	
Sorbic acid	Coating preservative	FCC
Vanillin	Flavouring agent	Ph Eur
Quinoline yellow	Colouring agent	
Ethanol 96%	Coating solvent	Ph Eur
Purified water	Coating solvent	Ph Eur

* dihydrate

4.2 PHARMACEUTICAL DEVELOPMENT

4.2.1 Components of the drug product

The tablet cores and coating formulations are based on a common percentage formula. The 8mg tablets used in the bioequivalence study were manufactured to the proposed formula.

Excipients were selected with consideration to those included in the Greek reference products. The function of each ingredient has been described. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies. Satisfactory results of excipient-active compatibility studies have been reported with no evidence of incompatibility seen in the excipients selected for inclusion in the tablets. The tablets are film-coated to protect the drug substance that is sensitive to light.

4.2.2 Formulation development

A satisfactory summary of the development of the product has been provided.

Satisfactory comparative in vitro dissolution profiles have been generated for batches of originator products from UK, Greece, Belgium, Germany and Nordic countries against the proposed 4mg and 8mg tablets.

4.2.3 Physicochemical and biological properties

A satisfactory summary of the physicochemical properties of the drug substance and processing needs of the formulation has been provided.

4.2.4 Manufacturing process development

A satisfactory summary of the development and scale-up studies has been provided that led to adoption of the direct compression process.

4.2.5 Container and closure system

Conventional PVC/Al blisters have been selected. This pack is suitable.

4.3 MANUFACTURE

4.3.1 Manufacturer(s)

A copy of the current Manufacturing Authorisation and GMP certificate has been provided for the proposed manufacturing and assembly site.

QC testing and batch release site:
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

A copy of the current manufacturing licence has been supplied.

4.3.2 Batch formula

Satisfactory formulae have been provided for the manufacture of a proposed maximum batch size. This is acceptable as the biobatch (lot 11) and other batches have been manufactured at a batch size greater than 10% of the proposed maximum batch size.

4.3.3 Description of manufacturing process and process controls

A flow chart of the manufacturing process has been provided. The manufacturing process is a standard direct compression method.

The maximum period for storage of the tablet cores prior to coating has been stated together with details of the storage conditions and packaging.

4.3.4 Control of critical steps and intermediates

Critical steps have been identified and in-process controls have been proposed. Satisfactory acceptance criteria have been established for the above tests.

4.3.5 Process validation and/or evaluation

The manufacturing process has been validated by manufacture of three batches of 4mg tablets and three batches of 8mg tablets manufactured in December 2001 and April 2002 at the proposed commercial site. Four batches of active substance (as proposed for the commercial products) were used. All in-process and end product test results meet the protocol limits and finished product specification limits.

A commitment has been provided that further process validation studies will be conducted on the first three commercial batches. Satisfactory acceptance criteria have been provided for these studies.

4.4 CONTROL OF EXCIPIENTS

4.4.1 Specifications

All excipients used in manufacture of the tablet cores are said to comply with Ph Eur monographs. Satisfactory specifications from the suppliers/finished product manufacturer have been provided to demonstrate that lactose monohydrate, pregelatinised starch, microcrystalline cellulose and ethanol 96% and purified water are tested for compliance with relevant Ph Eur monographs. The applicant has stated that between testing performed by the supplier and by the manufacturer of the finished product it can be demonstrated whether a specific batch of magnesium stearate complies with the requirements of the Ph Eur monograph. This is acceptable.

Satisfactory supplier and finished product manufacturer specifications have been provided for the commercial Opadry powder.

Satisfactory Certificates of Analysis have been provided.

4.4.2 Excipients of human or animal origin

The MAA forms state that lactose (as monohydrate) is a material of animal or human origin used in manufacture of the tablets.
It is stated that calf rennet is used in manufacture of the whey used in preparation of this source of lactose monohydrate. It is known that TSE risk is minimised in line with EMEA/CPMP/571/02. It has also been confirmed that the milk used for production of lactose is sourced from healthy cows under the same conditions as milk collected for human consumption.

No genetically modified organisms are included in these products.

4.5 CONTROL OF DRUG PRODUCT

4.5.1 Specification

The proposed finished product specifications have been provided.

Limits for impurities A, B, C and D have been included in the specification and are controlled in line with the limits in the Ph Eur monograph for ondansetron hydrochloride dihydrate and with the drug substance specification. Impurities E and F are process impurities controlled by the drug substance specification that have not been detected in batches of drug substance from the active substance manufacturer. It is therefore reasonable that limits have not been included in the finished product specification.

4.5.2 Analytical procedures / Validation of analytical procedures

Identification and assay of ondansetron and determination of impurities is by an HPLC method which has been validated.

The dissolution method has been suitably validated.

Levels of residual solvent (ethanol) are determined by an in-house method.

Microbial quality testing uses the methods described in the Ph Eur.

4.5.3 Batch analyses

Satisfactory batch analysis data have been provided for three batches of 4mg tablets and three batches of 8mg tablets manufactured in December 2001 and April 2002 at the proposed commercial site. All batches used drug substance from the active substance manufacturer as proposed for the commercial products. All batches comply with the proposed release specification.

4.5.4 Characterisation of impurities

Impurities A, B, C, D and HD-V are not found in batches of the active substance. Five unidentified impurities have been found in batches of active substance.

4.5.5 Justification of specifications

A justification for the release and shelf-life specifications has been provided.

4.6 REFERENCE STANDARDS OR MATERIALS

Satisfactory information on the reference standards of ondansetron hydrochloride and the impurities have been provided. These have all been characterised and are supported by Certificates of Analysis.

4.7 CONTAINER-CLOSURE SYSTEM

The tablets are presented in white opaque 250 μm PVC/20 μm aluminium blisters. The tablets will be presented in packs containing 3, 6, 10, 14, 15, 20, 30, 40, 50, 60, 90, 100, 200, 300 and 500 tablets. Not all pack sizes will be marketed. The packaging material is suitable for food use.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components. The PVC film complies with Directive 90/128/EEC. The extent of testing performed on receipt of consignments of packaging components has been stated and satisfactory acceptance criteria have been set. An identification test will be performed on all batches.

4.8 STABILITY

4.8.1 Stability summary and conclusion

Stability data have been provided for batches of 4mg tablets and 8mg tablets manufactured in December 2001 and April 2002 at the proposed commercial site. All batches used drug substance from the active substance manufacturer as proposed for the commercial products. All batches were stored in opaque white PVC/Al blisters as proposed for marketing.

The analytical methods were as described for routine batch release.

Stability data provided:	long-term and accelerated data
Test parameters:	appearance, identification, water content, hardness, assay, related substances (HPLC), disintegration, dissolution, seal integrity and microbial testing

No major changes were seen in samples stored under the above conditions. A number of unknown impurities were seen during storage, two of which increased over the storage period; however, levels of impurities remained within specification limits. The presence of unknown impurities may limit shelf-life.

The results of a forced degradation study have been provided.

The applicant has proposed a shelf-life of 24 months for product labelled with 'Do not store above 25°C'. Satisfactory data has been supplied to support this proposed shelf-life.

4.8.2 Post-approval stability protocol and stability commitment

A commitment has been provided that the first three production batches of each strength will be placed on store and that testing of the ongoing studies will continue.

4.9 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 64mg of ondansetron that may be the result of saturation of the first-pass metabolism.

Study number:	04/01 (January - April 2002)
Test product:	Ondansetron 8mg Film-coated Tablets (as proposed for marketing). Lot 11 (manufacturing date: December 2001; 100 000 tablets)
Reference product:	Zofron Tablets 8 mg (Glaxo Wellcome, Greece), Lot B017898

Certificates of Analysis have been provided for the test and reference batches; test results are satisfactory. In a comparative dissolution study all test and comparator tablets tested released more than 95% label claim within 20 minutes.

Table 4: Results from a two-way open randomised single-dose crossover study between the test and reference products, dosed fasted at a dose of 24mg. Log transformed; ANOVA; n=24 male subjects. Washout period 7 days between phases. tlast=24 hours

Test parameter	Test product	Reference product	Point estimate (%)	90% confidence intervals (%)
AUC_{0-t} (ng h/ml)	506.40 ± 193.10	500.38 ± 173.89	100.45	96.20 – 104.88
$AUC_{(24\ h)\ 0-\infty}$ (ng h/ml)	510.90 ± 201.72	500.38 ± 173.89	100.99	96.40 – 105.79
C_{max} (ng/ml)	83.10 ± 30.45	85.22 ± 30.27	97.39	92.88 – 102.12
T_{max} (h) *	1.65 ± 0.63	1.73 ± 0.73	-	-
$t_{½}$ *	3.91 ± 0.93	3.47 ±0.69	-	-

* non-parametric analysis

The above study was designed with a single dose of 24 mg (3 tablets) to ensure that over the course of the sampling period (24 hours) that is equivalent to 3-5 times the $t_{½}$, plasma levels would remain above the limit of quantitation of the method. This

has not been seen as necessary in other studies.

Studies have shown a non-proportional increase in systemic availability with doses increasing from 8mg up to 64mg suggesting a saturation of the first-pass metabolism. This raises questions over the suitability of comparing the test and comparator products at a dose of 32mg, especially given that this is outside of normal dosing practice. However, ondansetron is well absorbed and shows rapid and complete dissolution such that formulation differences are unlikely to be manifested in the PK profiles. Use of 24mg as the dose is accepted.

As the 90% confidence intervals for the mean $AUC_{0\text{-}t}$, $AUC_{(24\ h)0\text{-}\infty}$ and C_{max} values (following log transformation) are within 0.80-1.25%, the test and reference products may be considered bioequivalent, dosed to male subjects under fasting conditions.

Absence of a bioequivalence study on the 4mg tablets is accepted. Linear kinetics apply between 4mg and 8mg, proportional formulae for the tablets have been used and similar dissolution results have been shown for the two strengths. The criteria for biowaiver are satisfied.

Plasma concentrations of ondansetron were determined using a validated HPLC method. The method uses solid-phase extraction (cyanopropyl cartridge) of human plasma prepared in pH 4.2 sodium acetate buffer. Ondansetron was eluted with 1% ammonia solution in propan-2-ol. Dried extracts were reconstituted in pH 4.2 acetate buffer. A 7-point calibration curve was used to quantify the results from HPLC analysis with UV detection at 305nm. The method has been suitably validated over a range of 5-200ng/ml. This range covers all samples taken from the study. Limit of quantitation has been established at 5ng/ml. Plasma samples were stored at -20°C until analysed.

5. PRODUCT LITERATURE

5.1 SPC
The SPC is complete and in-line with the quality section and SPC guideline.

5.2 PIL
The PIL is complete and in-line with the SPC and relevant guidelines.

5.3 LABEL
The labels are complete and in-line with the SPC and relevant guidelines.

6. ADMINISTRATIVE

6.1 MAA form
The MAA is complete and in-line with the SPC and relevant guidelines.

6.2 Quality Overall Summary

The summary has been done by a suitably qualified person. The report is a summary of the module.

7. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

Please note that these applications for Ondansetron Tablets were submitted at the same time as applications for Ondansetron 2mg/ml Injections (PL 04543/0507-08) and were assessed concurrently. As such, the following assessment report refers to all products.

I INTRODUCTION

These are abridged national applications for Ondansetron 2 mg/ml Injection (4 mg in 2 ml), Ondansetron 2 mg/ml Injection (8 mg in 4 ml), Ondansetron 4 mg Tablets and Ondansetron 8 mg Tablets submitted by CP Pharmaceuticals Limited under Article 10.1(a)(iii) of Council Directive 2001/83/EC. Essential similarity is claimed to Zofran 2 mg/ml injection and Zofran 8 mg and 4 mg tablets, marketed by Glaxo Operations UK Limited and GlaxoWellcome (now GlaxoSmithKline) (PLs 00004/0375, 10949/0110 and 0111).

Ondansetron hydrochloride, a carbazole, is a selective inhibitor of type 3 serotonin (5-hydroxytryptamine) receptors (5-HT_3) that exhibits anti-emetic activity. The products are solutions for intravenous or intramuscular injection containing either 4 mg in 2 ml or 8 mg in 4 ml and film-coated tablets for oral consumption containing 4 mg or 8 mg ondansetron. They are intended 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 and children. The recommended dose for adults for injection or infusion is 8 – 32 mg per day administered as 8 mg immediately before chemotherapy or radiotherapy, followed by 8 mg orally twelve hourly. For the tablets, the dose is 8 mg two hours before treatment, followed by 8 mg twelve hours later. To protect against delayed or prolonged emesis, treatment should be continued for up to five days at a rate of 8 mg twice daily. These doses are equivalent to a maximum of 0.32 mg/kg per day in a 50 kg human. The dose for children is by the intravenous route is 5 mg/m^2 immediately before chemotherapy followed by 4 mg orally twelve hours later. Treatment should be continued for up to five days at a rate of 4 mg orally twice daily. For post-operative nausea and vomiting, the dose is 4 mg for adults and 0.1 mg/kg for children.

The applicant has provided Nonclinical Overviews but no supporting data.

I.1 Good Laboratory Practice (GLP) aspects

No preclinical studies have been conducted. Toxicity data from the originator's submission are cited and it is assumed that the studies would have been GLP-compliant. Other information has been taken from publications and their GLP status is unknown.

II PHARMACODYNAMICS / PHARMACOKINETICS / TOXICOLOGY

The actions of ondansetron have been characterised in previous submissions and will not be recapitulated in detail here.

Ondansetron is highly selective antagonist of 5-HT_3 receptors, with negligible agonist or antagonist activity on other 5-HT or non-5-HT receptor-containing tissues and considerably greater potency than metoclopramide. It also has weak affinity for other receptors such as the μ-opiate binding site and voltage-gated potassium channels. It is possible that these

additional properties are involved in ondansetron's anti-emetic effects in cancer chemotherapy. The data indicate that the anti-emetic effects of 5-HT_3 receptor antagonists are mediated principally via both peripheral (vagal) and central (hindbrain) sites.

In rats and dogs, oral absorption is rapid with t_{max} occurring at 30 and 40 minutes respectively. There is extensive first pass metabolism, resulting in low bioavailability and a short half-life. In humans, bioavailability is higher and systemic clearance is moderate. There is also evidence of saturation of first pass metabolism. The information provided on distribution relates mostly to humans: ondansetron has a large volume of distribution and is taken up by tissue membranes. It also distributes into erythrocytes, and penetrates the central nervous system in both humans and rats. The degree of plasma protein-binding is up to 76% and there is no significant binding to α-1-acid glycoprotein, the levels of which can increase in cancer patients. Hydroxylation and oxidation are the main routes of metabolism, followed by glucuronide or sulphate conjugation. Various cytochrome P_{450} isotypes are involved. The major route of elimination in animals is by metabolism with excretion in the bile, while in humans, the predominant route is via the urine.

The toxicity of the 5-HT_3 receptor antagonists, including ondansetron, is low with the main physical signs being decreased activity, ataxia and convulsions. There was no evidence of genetic, reproductive or end-organ toxicity. At high doses in long-term rodent studies, an increase in serum transaminases was found. There was no evidence of tumour induction in either rats or mice. Tests of local irritation showed no effects. In a guinea pig sensitisation study, there was no evidence of a reaction but hypersensitivity has been seen in a small number of patients, mostly following the first dose of the second or third cycle of chemotherapy. Probably related to ondansetron's affinity for the HERG potassium channel, a prolongation of cardiac repolarisation has been reported.

III EXCIPIENTS / IMPURITIES / RESIDUAL SOLVENTS

The excipients are all commonly used in injectable and tablet formulations and are listed in European Pharmacopoeial monographs.

The impurities and residual solvent are controlled at acceptable limits.

Assessor's comment
The published data include information on most of the aspects usually expected to be available from a preclinical development programme and essential similarity has been demonstrated. There is extensive clinical experience with ondansetron and the effects are well known; adequate warnings are proposed in the SPC regarding the risks.

IV NONCLINICAL OVERVIEWS

The nonclinical overviews were written by an appropriately qualified independent consultant. The overviews for the injectable and tablet formulations differed in that the former was very brief and relied on the demonstration of essential similarity. The latter was slightly more detailed and contains a review of over one hundred and forty references, including a publication by the originators on the toxicity investigations on ondansetron.

V SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Sections 4.6 and 5.3 are identical to those of the originator's SPC.

VI CONCLUSION

This application has not revealed any evidence of untoward toxicity from treatment with Ondansetron 2 mg/ml Injection (4 mg in 2 ml), Ondansetron 2 mg/ml Injection (8 mg in 4 ml), Ondansetron 4 mg Tablets and Ondansetron 8 mg Tablets, beyond the already well-described effects of ondansetron and adequate warnings are proposed. There is no objection to the grant of a licence from a preclinical point of view.

The SPC is acceptable from a pre-clinical point of view.

CLINICAL ASSESSMENT

1. INTRODUCTION and BACKGROUND

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 are two generic abridged applications for film coated tablets containing 4 and 8 mg ondansetron.

The two applications are submitted under the provisions of Directive 2001/83/EC Article 10 (1)(a)(iii)} claiming that the products are essentially similar to the proprietary products Zofran 4 mg & 8mg Tablets, that were authorised in the UK on 7/03/1990.

This is considered satisfactory.

The applications have been made in CTD format.

This is considered satisfactory.

The clinical data provided includes the study report of a randomised, 2-way crossover, bioequivalence study undertaken to characterise the relative bio-availability from three x 8 mg tablets of the reference product, Glaxo-Wellcome Zofron tablets, marketed in Greece, with three of the Company's proposed 8 mg tablets.

2. INDICATIONS

The proposed indication is consistent with the November 2004 SmPC for Zofran in the UK.

This is considered satisfactory.

3. DOSE & DOSE SCHEDULE

The proposed dose and dosage schedules for these products have been compared with the November 2004 version of the Summary of Product Characteristics for Zofran tablets in the UK.

The dosage schedules are considered satisfactory and are consistent with the SmPC for Zofran tablets PL 10949/0110-0111.

4. TOXICOLOGY

Not assessed.

5. CLINICAL PHARMACOLOGY

Pharmacokinetics

A comparative bioavailability study has been submitted.

This was a crossover study, protocol code no 04/01, to investigate the bioequivalence of two oral ondansetron preparations on the basis of their relative bioavailability following the oral administration of the test formulation Ondansetron/Pharmathen 8mg f.c tablets and reference formulation Zofron® 8mg f.c tablets, undertaken over the period January 2002 – April 2002.

Blood sampling was undertaken pre- and up to 24 h post administration.

Analysis of ondansetron plasma concentrations was by means of a validated HPLC method.

Statistical comparison of the preparations was based on the pharmacokinetic target parameters evaluated.

Twenty four healthy male volunteers from local population, aged between 18 and 42 years, body weight within +/- 15% of ideal body weight (according to MLIC) were enrolled in the study.

The test products were Ondansetron.Pharmathen Lot No. 11, Exp. Date: 12/2002 and Zofron ®, Glaxo Wellcome A.E.B.E Lot No. B017898, Exp. date 07/2003.

Three film coated tablets (total 24mg) of Ondansetron/Pharmathen or ZOFRON ® were administered in the two different test periods.

The comparator product was Zofron 8 mg tablets, Glaxo Welcome, UK, Batch No B017898, sourced from the UK. The applicant confirms that these Zofron Tablets were approved in Greece on 4th April 1990. The tablets were purchased in Greece and manufactured and packaged in the UK.

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 using EqivTest 1.0 statistical program.

The 90% confidence interval of the relative Cmax and AUC of the test to the reference Zofron product were within the 80-125% range. A copy of the key PK findings is presented below.

	Mean -/+ SD		
	Test	Reference	
AUC 0-last	447.59 +/-180.82 ng*h/ml	439.18+/-147.26ng*h/ml	
AUC (last) 0-∞	511.13 +/-198.87 ng*h/ml	501.63+/-169.90ng*h/ml	
AUC 0-last 0-24h	506.40 +/-193.10ng*h/ml	500.38+/-173.89ng*h/ml	
AUC 0-last (24h) 0-∞	510.90 +/-201.72 ng*h/ml	500.38+/-173.89ng*h/ml	
C max	83.10+/-30.45 ng/ml	85.22+/-30.27ng/ml	

All 90% confidence intervals were found to be within the limits of acceptance:

90%CI for the ratio μT/μR	
AUC 0-last	(0.9517, 1.0645)
AUC (last) 0-∞	(0.9586, 1.0619
AUC 0-last 0-24h	(0.9620, 1.0488)
AUC 0-last (24h) 0-∞	0.9640, 1.0579)

C max	(0.9288, 1.0212

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.

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

6. EFFICACY

No original data on the formulation proposed for marketing were submitted for assessment.

This is considered acceptable.

7. SAFETY

No original data on the formulation proposed for marketing submitted for assessment.

8. EXPERT REPORT

A Clinical Overview and information about the Expert-Clinical has been provided.

This is considered acceptable.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs for these products have been provided.

The text for sections 4 and 5 of the proposed SmPCs are considered satisfactory and consistent with the SmPCs for Zofran 4 and 8 mg tablets, PL 10949/0110-0111.

10. PATIENT INFORMATION LEAFLET

The proposed text for the PILs for these products have been provided and are considered consistent with the PILs for Zofran 4mg & 8mg Tablets PL 10949/0110-0111.

11. LABELLING

The proposed Labelling for these products have been provided and is considered satisfactory.

12. CONCLUSIONS

Overall there is no clinical objection to the grant of MAs for these two applications. No new or unexpected safety concerns arise from these applications. The proposed SmPC and PIL are considered satisfactory and are consistent with the SPCs and PILs for ZOFRAN 4mg & 8mg Tablets, PL 10949/0110-1.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

These applications have not revealed any evidence of untoward toxicity from treatment with Ondansetron 4mg and 8mg Tablets beyond the already well-described effects of ondansetron and adequate warnings are proposed.

EFFICACY

Bioequivalence has been demonstrated between the applicants Ondansetron Tablets and the originator products, Zofran Tablets.

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 data supplied supports the claim that the applicant's products and the innovator products are interchangeable. 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 TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0510

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 23/07/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 11/08/2004.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 17/06/2005 and 25/11/2005.
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 27/07/2005 and 07/12/2005.
5	The application was determined on 21/03/2006.

ONDANSETRON 4MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0510

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

ONDANSETRON 4MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Pale yellow, round, biconvex, film-coated tablets with '41' embossed on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ondansetron hydrochloride 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

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 hydrochloride should be flexible in the range of 8-32mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy: Ondansetron hydrochloride can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron hydrochloride 8mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

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

Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g.. high-dose cisplatin, Ondansetron hydrochloride can be given either by rectal, intravenous or intramuscular administration.

Ondansetron hydrochloride has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy.
- A dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A single dose of 32mg diluted in 50-l00ml of saline or other compatible infusion fluid *(see Pharmaceutical Precautions)* and infused over not less than 15 minutes immediately before chemotherapy.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of ondansetron hydrochloride in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy.

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

Children: Ondansetron hydrochloride 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 five days after a course of treatment.

Elderly: Ondansetron hydrochloride 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 hydrochloride 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 hydrochloride can be administered orally or by intravenous or intramuscular injection.

Ondansetron hydrochloride may be administered as a single dose of 4mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over): For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, Ondansetron may be administered by slow intravenous injection at a dose of 0.lmg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia. For treatment of established PONV in paediatric patients, Ondansetron may be administered by slow intravenous injection at a dose of 0.lmg/kg up to a maximum of 4mg.

There is limited data on the use of ondansetron hydrochloride in the prevention and treatment of PONV in children under two years of age.

Elderly: There is limited experience in the use of ondansetron hydrochloride in the prevention and treatment of PONV in the elderly, however ondansetron hydrochloride 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 hydrochloride 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 hydrochloride 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.

4.4. Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HTs 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, temazepan, furosemide, tramadol or propofol.

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

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

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

4.6. Pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and pre- 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 hydrochloride 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

Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. The following side effects can occur: headache, a sensation of flushing or warmth, hiccups and occasional asymptomatic increases in liver function tests. There have been rare reports of immediate hypersensitivity reactions sometimes severe including anaphylaxis. Rare cases of transient visual disturbances (e.g. blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron. There have been rare reports suggestive of involuntary movement disorders such as extrapyramidal reactions e.g. oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects. Chest pain with or

without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

Occasionally, hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

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

ATC code:- A04 Antiemetics and antinauseants
ATC group:- A04AA0 1 Serotonin ($5HT_3$) antagonist

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

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

5.2. Pharmacokinetic Properties

Following oral administration, 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 (five 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 three 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 five 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 20-30ng/ml are attained, typically six 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 six 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 three 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 (three -seven years old) or 4mg (eight -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 l00mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at three years. Use of weight-based dosing (0.lmg/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

Cores
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Magnesium stearate

Film Coating
Hypromellose
Titanium dioxide
Hyprolose
Propylene gylcol
Sorbitan monooleate
Sorbic acid
Vanillin
Quinoline yellow

6.2. Incompatibilities

None reported.

6.3. Shelf life

Two years

6.4. Special precautions for storage

Do not store above 25°C.

Keep out of the reach and sight of children.

6.5. Nature and contents of container

PVC/PVDC/aluminium foil opaque blister packs containing 7, 14, 28, 30 or 100* tablets.

*Not all pack sizes may be marketed

6.6. Instructions for use and handling

None stated.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd (Trading as Wockhardt UK)
Ash Road North
Wrexham LL13 9UF
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Pl 04543/ 0509

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st March 2006

10. DATE OF REVISION OF THE TEXT

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE) PL 04543/0510

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 8mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8mg of ondansetron (as hydrochloride dihydrate).

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

Pale yellow, round, biconvex , film-coated tablets with '42' embossed on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ondansetron hydrochloride 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

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 hydrochloride should be flexible in the range of 8-32mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy: Ondansetron hydrochloride can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron hydrochloride 8mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

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

Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g.. high-dose cisplatin, Ondansetron hydrochloride can be given either by rectal, intravenous or intramuscular administration.

Ondansetron hydrochloride has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy.
- A dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A single dose of 32mg diluted in 50-l00ml of saline or other compatible infusion fluid *(see Pharmaceutical Precautions)* and infused over not less than 15 minutes immediately before chemotherapy.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of ondansetron hydrochloride in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy.

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

Children: Ondansetron hydrochloride 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 five days after a course of treatment.

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

<u>Post-operative nausea and vomiting (PONV):</u>

Adults: For the prevention of PONV ondansetron hydrochloride can be administered orally or by intravenous or intramuscular injection.

Ondansetron hydrochloride may be administered as a single dose of 4mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over): For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, Ondansetron may be administered by slow intravenous injection at a dose of 0.lmg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia. For treatment of established PONV in paediatric patients, Ondansetron may be administered by slow intravenous injection at a dose of 0.lmg/kg up to a maximum of 4mg.

There is limited data on the use of ondansetron hydrochloride in the prevention and treatment of PONV in children under two years of age.

Elderly: There is limited experience in the use of ondansetron hydrochloride in the prevention and treatment of PONV in the elderly, however ondansetron hydrochloride 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 hydrochloride 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 hydrochloride 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.

4.4. Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HTs 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, temazepan, furosemide, tramadol or propofol.

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

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

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

4.6. Pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and pre- 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 hydrochloride 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

Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. The following side effects can occur: headache, a sensation of flushing or warmth, hiccups and occasional asymptomatic increases in liver function tests. There have been rare reports of immediate hypersensitivity reactions sometimes severe including anaphylaxis. Rare cases of transient visual disturbances (e.g. blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron. There have been rare reports suggestive of involuntary movement disorders such as extrapyramidal reactions e.g. oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological

mechanism can account for ondansetron causing these effects. Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia have been rarely reported.

Occasionally, hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

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

ATC code:- A04 Antiemetics and antinauseants
ATC group:- A04AA0 1 Serotonin ($5HT_3$) antagonist

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

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

5.2. Pharmacokinetic Properties

Following oral administration, 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 (five 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 three 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 five 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 20-30ng/ml are attained, typically six 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 six 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 three 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 (three -seven years old) or 4mg (eight -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 l00mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at three years. Use of weight-based dosing (0.lmg/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

Cores
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Magnesium stearate

Film Coating
Hypromellose
Titanium dioxide
Hyprolose
Propylene gylcol
Sorbitan monooleate
Sorbic acid
Vanillin
Quinoline yellow

6.2. Incompatibilities

None reported.

6.3. Shelf life

Two years

6.4. Special precautions for storage

Do not store above 25°C.

Keep out of the reach and sight of children.

6.5. Nature and contents of container

PVC/PVDC/aluminium foil opaque blister packs containing 7, 14, 28, 30 or 100* tablets.

*Not all pack sizes may be marketed

6.6. Instructions for use and handling

None stated.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL12 8NE
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Pl 04543/ 0510

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st March 2006

10. DATE OF REVISION OF THE TEXT

ONDANSETRON 4MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0510

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET

ONDANSETRON 4MG OR 8MG TABLETS
Ondansetron hydrochloride dihydrate tablets

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

In this leaflet:

The active substance in the tablets is ondansetron (as hydrochloride dihydrate). Each 4mg tablet contains 4mg of ondansetron (as hydrochloride dihydrate). Each 8mg tablet contains 8mg of ondansetron (as hydrochloride dihydrate).

The other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, magnesium stearate, hypromellose, titanium dioxide, hyprolose, propylene glycol, sorbitan monooleate, sorbic acid, vanillin and quinoline yellow.

Ondansetron tablets are manufactured by the Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF

1. WHAT IS ONDANSETRON AND WHAT IT IS USED FOR

Ondansetron 4mg tablets are pale yellow, round, biconvex, film-coated tablets with '41' embossed on one side. Ondansetron 8mg tablets are pale yellow, round, biconvex, film-coated tablets with '42' embossed on one side. They are available in blister packs containing 28 tablets.

Ondansetron (as hydrochloride dihydrate) belongs to a group of medicines known as anti-emetics.

Some other medicines which you have been given or are taking can make you feel sick or be sick. Ondansetron tablets are used to stop you feeling or being sick. They can also be used to stop you feeling or being sick after you have had an operation.

2. BEFORE YOU TAKE ONDANSETRON TABLETS

You should not take ondansetron tablets:

- if you are allergic to ondansetron or any of the other ingredients

Special care is required if:

- if you are allergic to any similar drugs known as $5HT_3$ receptor-antagonists
- if you have a blockage of the bowels

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Taking tablets with food and drink:

It does not matter when you take your tablets in relation to food.

Pregnancy

You should not take ondansetron if you are pregnant. You should let your doctor know if you think you may be pregnant or are trying for a baby.

Breast-feeding

You should not breast-feed while taking ondansetron tablets.

Driving and using machines:

Ondansetron tablets should not affect your ability to drive or use machines. However, if you are affected, do not drive or operate machinery.

Important information about some of the ingredients of ondansetron tablets:

Ondansetron tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, check with your doctor before taking ondansetron tablets.

Taking other medicines:

Care is required if ondansetron tablets are taken at the same time as:-

- Phenytoin and carbamazepine, drugs used to treat epilepsy
- Rifampicin, a drug used to treat infections
- Tramadol, a pain-killer

Tell your doctor or pharmacist about medicines you are currently taking or have taken recently. This also applies to medicines you may have bought yourself from a pharmacy or supermarket.

3. HOW TO TAKE ONDANSETRON TABLETS

For oral use.

For treatment for feeling sick or being sick in patients receiving chemotherapy and/or radiotherapy

Adults (including the elderly):

The usual dose is 8mg of ondansetron two hours before your treatment, followed by 8mg 12 hours later. You may have to take the tablets twice a day for up to five days.

Children:

The usual dose is 4mg of ondansetron, followed by 4mg twice a day for up to five days.

For prevention of feeling sick or being sick after an operation

Adults (including the elderly):

The usual dose is 16mg of ondansetron one hour before your anaesthetic or 8mg of ondansetron one hour before your anaesthetic followed by two 8mg doses eight hours apart.

Ondansetron tablets are not recommended for this sort of treatment in children.

If you have liver problems you may be advised not to take more than 8mg of ondansetron in one day.

Your doctor will decide the dose that is best for you. Always follow your doctor's instructions completely. Also, follow any instructions or warnings that appear on the label that the pharmacist has put on the pack. If you do not understand, or are in any doubt, ask your doctor or pharmacist.

To obtain a tablet, press on the tablet from the blister (or bubble) side, pushing it through the foil. Do not remove the tablet from the blister until you are ready to take it.

Unless told otherwise, take your tablets with water.

If you take more tablets than you should:

If you or anybody else takes too many tablets, you should contact your doctor, pharmacist or nearest hospital casualty department immediately. Take this leaflet and any tablets you have left to show the doctor or pharmacist.

If you forget to take ondansetron tablets:

If you forget to take a dose and are feeling sick or being sick, take the dose as soon as possible. If you miss a dose but are not feeling sick or being sick, just take the next dose when it is due. Never double the next dose to make up for the one missed. Do not stop taking the medicine without talking to your doctor first.

4. POSSIBLE SIDE EFFECTS

Like any other medication, ondansetron may cause side-effects. These include constipation, headache, flushing, feeling warm and hiccups.

Rarely, changes in liver function, blurred vision, and dizziness have been reported.

Very rarely, abnormal body movements with stiffness and shaking, heart problems and problems with blood pressure have been reported.

Rarely, allergic reactions can occur. **You should tell your doctor immediately** if you develop wheezing, difficulty breathing, a skin rash, itching, or swelling of your lips, eyes or tongue.

If you notice any side effects not mentioned in this leaflet, or feel that the medicine is affecting you badly, please inform your doctor or pharmacist.

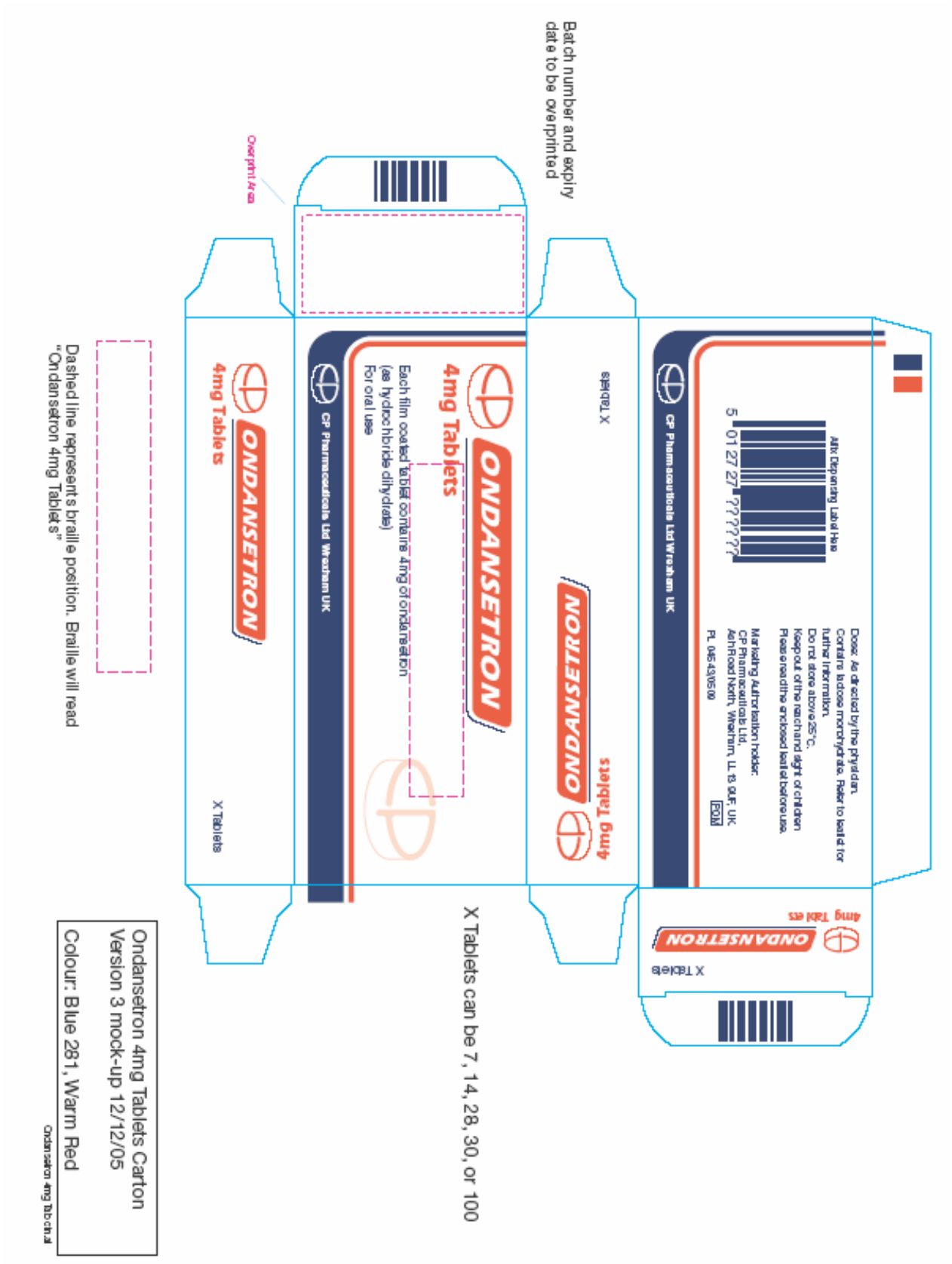
5. STORING ONDANSETRON TABLETS

Keep out of the reach and sight of children.
Do not store above 25°C.
Do not use after the expiry date stated on the carton.
Do not take ondansetron tablets if you notice they are discoloured (they should be pale yellow).

This leaflet was last approved on 21st March 2006

ONDANSETRON 4MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0509

LABELLING



FOIL

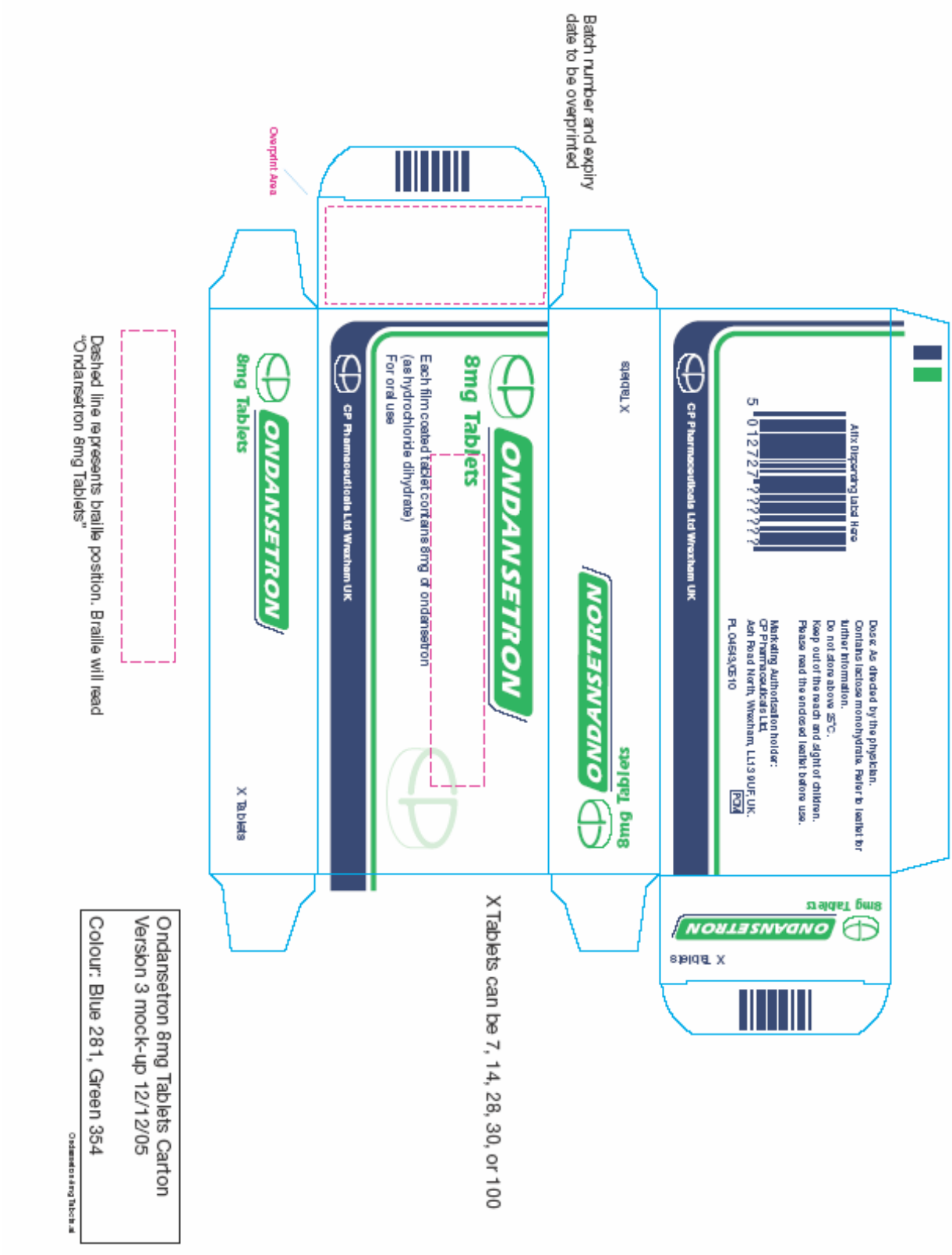
Overprint area

Batch number and expiry date to be overprinted

ONDANSETRON 8MG TABLETS (ONDANSETRON HYDROCHLORIDE)
PL 04543/0510

LABELLING

CARTON



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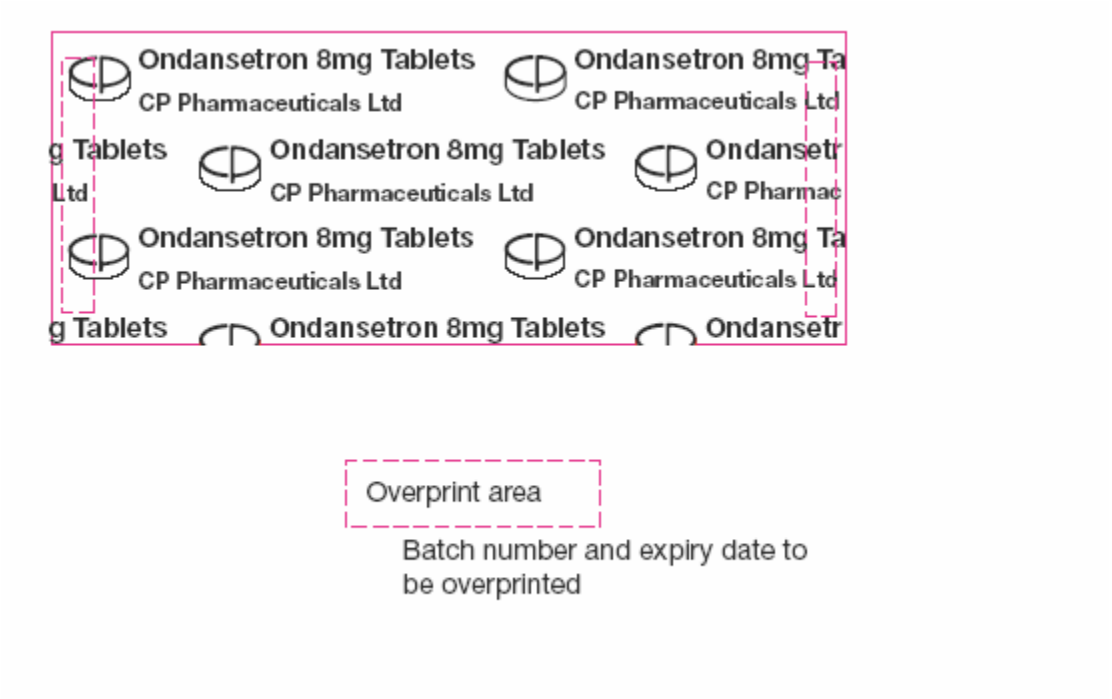
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