

**ONDANSETRON 4MG/2ML INJECTION
(ONDANSETRON HYDROCHLORIDE)
PL 04543/0507**

**ONDANSETRON 8MG/4ML INJECTION
(ONDANSETRON HYDROCHLORIDE)
PL 04543/0508**

UKPAR

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PL 04543/0508**

LAY SUMMARY

The MHRA granted CP Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal product Ondansetron 4mg/2ml injection (PL 04543/0507) and Ondansetron 8mg/4ml Injection (PL 04543/0508) on 21st March 2006. This prescription only medicine (POM) is 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 Injections 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 2mg/ml Injections (4mg in 2ml and 8mg in 4ml) are equivalent to the approved product, Zofran 2mg/ml Injection. Ondansetron 2mg/ml Injections can therefore be used interchangeably with Zofran 2mg/ml Injection.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Ondansetron 2mg/ml Injections outweigh the risks. Hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Ondansetron 4mg/2ml Injection (PL 04543/0507) and Ondansetron 8mg/4ml Injection (PL 04543/0508) to CP Pharmaceuticals Limited on 21st March 2006. The product is a prescription only medicine.

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 product Zofran 2mg/ml Injection.

The product contains the active ingredient ondansetron hydrochloride and is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of post operative nausea and vomiting in adults and children.

Ondansetron hydrochloride, a carbazole, is a selective inhibitor of type 3 serotonin (5-hydroxytryptamine) receptors (5-HT₃) 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 product, Zofran 2mg/ml injection (PL 00004/0375), was licensed in the UK on the 7th March 1990, to GlaxoSmithKline.

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

C₁₈H₁₉N₃O. HCl. 2H₂O

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 20 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.

The synthetic route is 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 specification 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 (as stated in Module 1)

Ingredient	Function	Reference Standard
Ondansetron hydrochloride dihydrate (equivalent to ondansetron)	Active ingredient	Ph Eur
Citric acid monohydrate	Buffering agent	Ph Eur
Sodium citrate	Buffering agent	Ph Eur
Sodium chloride	Isotonicity agent	Ph Eur
Water for injections	Solvent/diluent	Ph Eur

4.2 PHARMACEUTICAL DEVELOPMENT

4.2.1 Components of the drug product

Composition of the proposed product is based on the reference product and the manufacturing process. A satisfactory summary of product development has been provided.

Results of active substance - excipient compatibility studies have been conducted that confirm compatibility. Sensitivity to light of ondansetron has been demonstrated in solid mixes and in solution.

Brief discussion on reasons for inclusion of the ingredients has been provided. The levels are typical for a product of this nature.

4.2.2 Formulation development

A satisfactory summary of the development of the product has been provided including the result of the manufacture of three laboratory-scale batches.

4.2.3 Physicochemical and biological properties

A satisfactory summary of the physicochemical properties of the drug substance has been provided.

One pseudo polymorph melting at 213°C has been found. Ondansetron manufactured by the active substance manufacturer corresponds to the polymorphic form with a melting range of 178-182°C.

4.2.4 Manufacturing process development

A satisfactory summary of the development and scale-up studies has been provided.

4.2.5 Container and closure system

3ml and 4ml amber Type I glass ampoules are used. Amber glass is selected to provide protection from light. The originator product is packed in clear glass ampoules. This pack is suitable.

4.3 MANUFACTURE

4.3.1 Manufacturer(s)

A copy of the current Manufacturing Authorisation has been provided for the proposed manufacturing and assembly site together with a GMP Certificate.

Batch release in the UK will be performed by CP Pharmaceuticals Ltd, Ash Road North, Wrexham. A valid Manufacturers Licence has been supplied.

4.3.2 Batch formula

Satisfactory formulae have been provided for the manufacture of the proposed maximum batch size.

4.3.3 Description of manufacturing process and process controls

A copy of a flow chart of the manufacturing process has been provided. The process can be summarised as follows:

Stage 1: Preparation of the solution (class C area):

Stage 2: Filtration:

Stage 3: Filling/sealing:

Stage 4: Sterilisation:

4.3.4 Control of critical steps and intermediates

Critical steps have been identified and proposed in-process controls and limits are acceptable.

4.3.5 Process validation and/or evaluation

The manufacturing process is straightforward using standard techniques with terminal sterilisation using overkill conditions.

Two batches of active substance have been used to manufacture batches of both presentations of the finished product in April 2002. The critical parameters previously described have been studied. Satisfactory results have been provided for in-process tests and finished product testing. As the conditions used for terminal sterilisation are pharmacopoeial conditions, it is not necessary to provide further data on validation of the process.

The manufacturer has provided a commitment that further process validation studies will be conducted on the first three commercial batches. This is acceptable. Process validation protocols for these studies have been provided.

4.4 CONTROL OF EXCIPIENTS

4.4.1 Specifications

All ingredients are said to comply with Ph Eur monographs.

4.4.2 Excipients of human or animal origin

No materials of animal origin are contained in or used in the manufacture of this product.

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

A monograph for Ondansetron Injection is included in USP 26.

4.5.2 Analytical procedures / Validation of analytical procedures

Identification and assay of ondansetron and determination of impurities is by HPLC. The methods have been validated.

Sterility is determined according to the cartridge filter method as described in the Ph Eur. The method has been validated.

The Ph Eur LAL method for bacterial endotoxins has been validated.

Satisfactory Certificates of Analysis have been provided for the ondansetron hydrochloride dihydrate working reference standard and impurities A, B, C, D and

HD-V.

4.5.3 Batch analyses

Satisfactory batch analysis data have been provided for three batches of each fill volume manufactured at the proposed commercial site in April 2002. All batches comply with the proposed release specification.

4.5.4 Characterisation of impurities

Potential impurities in the finished product are:

Impurity A: 3-[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-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: 1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one

Impurity D: 1,2,3,9-tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one

Impurity E: 1H-imidazole

Impurity F: 2-methyl-1H-imidazole

Impurity G: (3RS)-3-[(1H-imidazole-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

Impurity HD-V: 1,2,3,9-tetrahydro-9-methyl-3-[1-imidazol-1-yl]-4H-carbazol-4-one, reported throughout is the same as impurity G

However, none of the impurities have been found in batches of the finished product. Based on the stability results two unknown impurities are seen. Levels of these impurities do not show significant increase on storage.

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. All reference standards are provided by the active substance manufacturer, except for impurity B. These have all been characterised and are supported by Certificates of Analysis.

4.7 CONTAINER-CLOSURE SYSTEM

The product is presented in 3ml and 4ml capacity amber transparent Type I glass ampoules containing 2ml and 4ml solution, respectively. Ampoules are supplied in packs of 1, 2, 5 and 10 ampoules.

The ampoules meet the requirements of the Ph Eur for Type I glass and for glass

containers for pharmaceutical use. Levels of lead, cadmium, mercury and extravalent chromium do not exceed 100 ppm in accordance with EC 94/62. No materials containing asbestos are used in the manufacturing plant.

The ampoules are provided closed following dry heat sterilisation at 600°C.

Drawings with labelling in Greek have been provided for both sizes of ampoules. A Certificate of Conformity has been provided, although this provides little information.

Satisfactory specifications have been provided.

4.8 STABILITY

4.8.1 Stability summary and conclusion

Stability data have been provided for batches of each presentation manufactured in April 2002 and filled to a 2ml and 4ml nominal fill volume in the proposed commercial ampoules in cartons. Two batches of active substance were used in the manufacture of these batches.

Analytical methods used were as described for routine batch release.

Stability data provided: long-term and accelerated conditions

Test parameters: appearance, identification, pH, assay, related substances, average volume per ampoule, ampoule integrity, optical control on filled ampoule

Only minor changes attributable to analytical variation were seen in samples stored under both long-term and accelerated conditions. All individual impurities and total impurity levels were within specification limits.

The applicant has proposed a shelf-life of 24 months for product labelled with 'Do not store above 25°C'. As the data support extrapolation of the 12 months data, the proposed shelf-life is acceptable.

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 to continue the current tests.

4.9 BIOEQUIVALENCE/BIOAVAILABILITY

Bioequivalence studies are not necessary to support this application. The requirements of essential similarity are met with respect to qualitative and quantitative content of the drug substance (including comparative impurity profiles). Given the route of administration, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

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 2mg/ml Injections were submitted at the same time as applications for Ondansetron 4mg and 8mg Tablets (PL 04543/0509-10) and were assessed concurrently. As such, the following assessment report refers to all four 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-HT₃) 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/m² 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-HT₃ 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-HT₃ 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 P₄₅₀ 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-HT₃ 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 national abridged MAA.

The applications are submitted under the provisions of Article 10.1 (a) (iii) claiming that the products are essentially similar to the proprietary product Zofran 2mg/ml injectable solution, GlaxoSmithkline, approved in the UK in 1990. Zofran injection, ondansetron hydrochloride 2 mg/ml, PL 00004/0375, was granted a UK MA on 7/03/1990.

No clinical pharmacology data or clinical trials data have been submitted to directly support the claim of essentially similar of the proposed product to the proprietary product Zofran injection.

This is considered acceptable. See below.

The MAA has been made in CTD format.

2. INDICATIONS

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

This is considered satisfactory.

3. DOSE & DOSE SCHEDULE

The proposed dose and dosage schedules for this product has been compared with the Summary of Product Characteristics approved for Zofran in the UK in November 2004.

This is considered satisfactory. The dosage schedules are consistent with the current SmPC for Zofran 2 mg/ml injection, PL 00004/0375.

4. TOXICOLOGY

Not assessed.

5. CLINICAL PHARMACOLOGY

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

A Clinical Overview has been submitted. This states that the formulation of the proposed product is identical to the Glaxosmithkline formulations for injection of ondansetron.

Based on published CPMP guidelines on this topic, the similarity of formulations and the proposed route of administration are considered adequate justification for not undertaking a bioequivalence study.

This is considered satisfactory.

6. EFFICACY

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

This is considered acceptable.

7. SAFETY

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

This is considered acceptable. No new or unexpected safety concerns are considered to arise from these MAAs.

8. EXPERT REPORT

A Clinical Overview has been provided.

Information about the Expert-Clinical has been provided.

This is considered acceptable.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is consistent with the current SmPC for Zofran 2 mg/ml injection, PL 00004/0375.

10. PATIENT INFORMATION LEAFLET

The PIL is consistent with the PIL for Zofran 2 mg/ml injection, PL 00004/0375.

11. LABELLING

Satisfactory. Consistent with the proposed SmPC and the labelling regulations.

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 SPC and PIL for ZOFRAN, PL 00004/0375.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 2mg/ml injection 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 2 mg/ml Injection, beyond the already well-described effects of ondansetron and adequate warnings are proposed.

EFFICACY

The requirements of essential similarity to Zofran Injection are met with respect to qualitative and quantitative content of the drug substance.

No new or unexpected safety concerns arise from these applications.

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

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.

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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 10/08/2004.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 17/06/2005 and 19/08/2005.
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 27/07/2005 and 30/08/2005.
5	The application was determined on 21/03/2006.

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**ONDANSETRON 4MG/2ML INJECTION (ONDANSETRON HYDROCHLORIDE)
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2mg of ondansetron (as hydrochloride dihydrate)
Each 2ml ampoule contains 4mg of ondansetron (as hydrochloride dihydrate)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution, free from particles.

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 (PONV).

4.2. Posology and method of administration

Chemotherapy and Radiotherapy

For intravenous use or for intramuscular use. Refer to Section 6.6 'Instructions for Use and Handling', for information on compatibility with intravenous fluids and other drugs.

For single use. Discard any unused product immediately after use

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 50-100ml 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/m² 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 0.1mg/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 0.1mg/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 5HT₂ receptor antagonists. As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

This medicinal product contains less than 1mmol (23mg) of sodium in each ampoule. It is essentially 'sodium-free'.

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

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

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

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

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

4.6. Pregnancy and lactation

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:- A04AAO 1 Serotonin (5HT₃) antagonist

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

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

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

5.2. Pharmacokinetic Properties

Following oral administration, 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 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at three years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

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

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

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

5.3. Preclinical safety data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Water for injections.

6.2. Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

6.3. Shelf life

Two years

After dilution, see section 6.4 Special precautions for storage.

6.4. Special precautions for storage

Do not store above 25°C.
Keep the ampoule in the outer carton
Keep out of the reach and sight of children

After dilution:-

Chemical and physical in use stability has been demonstrated for 24 hours at 25°C and 5°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5. Nature and contents of container

Type I Ph Eur amber glass 3ml capacity ampoules. Each pack contains one or ten ampoules.

6.6. Instructions for use and handling

For single use. Discard any unused product immediately after use.

Ondansetron injection should not be autoclaved.

Compatibility with intravenous fluids:

Ondansetron injection should only be admixed with those infusion solutions which are recommended-

Sodium Chloride Intravenous Infusion BP 0.9%w/v

Glucose Intravenous Infusion BP 5%w/v

Mannitol Intravenous Infusion BP 10%w/v

Ringers Intravenous Infusion

Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP

Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

In keeping with good pharmaceutical practice dilutions of Ondansetron Injection in intravenous fluids should be prepared at the time of infusion, although chemical and physical in use stability after dilution has been demonstrated for 24 hours at 25°C and 5°C.

Compatibility with other drugs: Ondansetron may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for

ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively):

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil: Concentrations up to 0.8 mg/ml (e.g. 2.4g in 3 litres or 400mg in 500ml) administered at a rate of at least 20ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin: Concentrations in the range 0.18mg/ml to 9.9mg/ml (e.g. 90mg in 500ml to 990mg in 100ml), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72mg in 500ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5ml for 250mg and 10ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100mg to 1g, reconstituted with Water for Injections BP, 5ml per 100mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10-100mg reconstituted with Water for Injections BP, 5ml per 10mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over two to five minutes via the Y-site of an infusion set delivering 8 or 32mg of ondansetron diluted in 50-100ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 micrograms to 2.5mg/ml for dexamethasone sodium phosphate and 8 micrograms to 1mg/ml for ondansetron.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL13 9UF
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PI 04543/0507

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

21st March 2006

10. DATE OF REVISION OF THE TEXT

**ONDANSETRON 8MG/4ML INJECTION (ONDANSETRON HYDROCHLORIDE)
PL 04543/0508**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2mg of ondansetron (as hydrochloride dihydrate)

Each 4ml ampoule contains 8mg of ondansetron (as hydrochloride dihydrate)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution, free from particles

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 (PONV).

4.2. Posology and method of administration

Chemotherapy and Radiotherapy

For intravenous use or for intramuscular use. Refer to Section 6.6 'Instructions for Use and Handling', for information on compatibility with intravenous fluids and other drugs.

For single use. Discard any unused product immediately after use

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 50-100ml 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/m² 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 0.1mg/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 0.1mg/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 5HT₂ receptor antagonists. As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

This medicinal product contains less than 1mmol (23mg) of sodium in each ampoule. It is essentially 'sodium-free'.

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:- A04AAO 1 Serotonin (5HT₃) antagonist

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

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

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

5.2. Pharmacokinetic Properties

Following oral administration, 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 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at three years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

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

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

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

5.3. Preclinical safety data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Water for injections.

6.2. Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

6.3. Shelf life

Two years

After dilution, see section 6.4 Special precautions for storage.

6.4. Special precautions for storage

Do not store above 25°C.
Keep the ampoule in the outer carton
Keep out of the reach and sight of children

After dilution:-
Chemical and physical in use stability has been demonstrated for 24 hours at 25°C and 5°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5. Nature and contents of container

Type I Ph Eur amber glass 4ml capacity ampoules. Each pack contains one or ten ampoules.

6.6. Instructions for use and handling

For single use. Discard any unused product immediately after use.

Ondansetron injection should not be autoclaved.

Compatibility with intravenous fluids:

Ondansetron injection should only be admixed with those infusion solutions which are recommended-

Sodium Chloride Intravenous Infusion BP 0.9%w/v
Glucose Intravenous Infusion BP 5%w/v
Mannitol Intravenous Infusion BP 10%w/v
Ringers Intravenous Infusion
Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP
Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

In keeping with good pharmaceutical practice dilutions of Ondansetron Injection in intravenous fluids should be prepared at the time of infusion, although chemical and physical in use stability after dilution has been demonstrated for 24 hours at 25°C and 5°C.

Compatibility with other drugs: Ondansetron may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively):

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil: Concentrations up to 0.8 mg/ml (e.g. 2.4g in 3 litres or 400mg in 500ml) administered at a rate of at least 20ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin: Concentrations in the range 0.18mg/ml to 9.9mg/ml (e.g. 90mg in 500ml to 990mg in 100ml), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72mg in 500ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5ml for 250mg and 10ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100mg to 1g, reconstituted with Water for Injections BP, 5ml per 100mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10-100mg reconstituted with Water for Injections BP, 5ml per 10mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over two to five minutes via the Y-site of an infusion set delivering 8 or 32mg of ondansetron diluted in 50-100ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 micrograms to 2.5mg/ml for dexamethasone sodium phosphate and 8 micrograms to 1mg/ml for ondansetron.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL13 9UF
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PI 04543/0508

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st March 2006

10. DATE OF REVISION OF THE TEXT

**ONDANSETRON 4MG/2ML INJECTION (ONDANSETRON HYDROCHLORIDE)
PL 04543/0507**

**ONDANSETRON 8MG/4ML INJECTION (ONDANSETRON HYDROCHLORIDE)
PL 04543/0508**

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET

ONDANSETRON 2MG/ML SOLUTION FOR INJECTION

Ondansetron (as hydrochloride dihydrate) solution for injection

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

In this leaflet:

1. What is ondansetron (as hydrochloride dihydrate) and what is it used for?
2. Before you are given ondansetron
3. How ondansetron will be given to you
4. Possible side effects
5. Storing ondansetron

The active substance in the injection is ondansetron (as hydrochloride dihydrate). Each ml contains 2mg of ondansetron (as hydrochloride dihydrate). Each 2ml ampoule contains 4mg of ondansetron (as hydrochloride dihydrate) and each 4ml ampoule contains 8mg of ondansetron (as hydrochloride dihydrate).

The other ingredients are citric acid monohydrate, sodium citrate, sodium chloride and water for injections.

Ondansetron 2mg/ml Solution for Injection is manufactured by the Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF.

1. WHAT IS ONDANSETRON 2MG/ML SOLUTION FOR INJECTION AND WHAT IS IT USED FOR?

Ondansetron 2mg/ml Solution for Injection is a clear, colourless solution for injection which can also be diluted before use.

It is available in packs of one, five or ten amber glass ampoules containing 2ml (4mg) and 4ml (8mg) of solution for injection.

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 solution for injection is used to stop you feeling or being sick. It can also be used to stop you feeling or being sick after you have had an operation.

2. BEFORE YOU ARE GIVEN ONDANSETRON 2MG/ML SOLUTION FOR INJECTION

You will not be given ondansetron solution for injection:

- if you are allergic to ondansetron (as hydrochloride dihydrate) or any of the other ingredients

Your doctor will take special care when giving you ondansetron solution for injection:

- if you are allergic to any similar drugs known as 5HT₃ 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.

Pregnancy

Ondansetron injection should not be given to you 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 during ondansetron treatment.

Driving and using machines:

Ondansetron 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 solution for injection:

Ondansetron solution for injection contains less than 1mmol (23mg) of sodium in each ampoule. It is essentially 'sodium-free'.

Taking other medicines

Care is required if ondansetron solution for injection is administered 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 WILL ONDANSETRON 2MG/ML SOLUTION FOR INJECTION BE GIVEN TO YOU

Your injection will be given to you by a doctor or nurse. The solution can be injected directly into a muscle (intramuscularly), be given by a slow injection into a vein (intravenously) over several minutes or diluted with another fluid and given by a drip over a longer period of time.

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 given by slow intravenous or intramuscular injection immediately before your treatment.

This may be followed with two further doses of 8mg of ondansetron given by slow intravenous injection or intramuscular injection two to four hours apart or an infusion of 1mg/hour for up to 24 hours. Alternatively a dose of 32mg of ondansetron can be diluted in 50-

100ml of an infusion fluid and be given by infusion over at least 15 minutes, immediately before your chemotherapy.

Children:

The usual dose is a single dose of 5mg per square metre body surface given immediately before treatment.

For prevention of feeling sick or being sick after an operation

Adults (including the elderly):

The usual dose is 4mg of ondansetron given by intramuscular injection or slow intravenous injection at the same time as your anaesthetic.

Children aged two years and over:

The usual dose is 0.1mg per kg of bodyweight by slow intravenous injection (maximum 4mg) before or at the same time as your anaesthetic.

For treatment of feeling sick or being sick after an operation

Adults (including the elderly):

The usual dose is 4mg of ondansetron given by intramuscular injection or slow intravenous injection.

Children aged two years and over:

The usual dose is 0.1mg per kg of bodyweight by slow intravenous injection (maximum 4mg).

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

Your doctor will decide the dose which is best for you. If you do not understand, or are in any doubt, ask your doctor or nurse.

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.

Occasionally the area around where the needle is injected can become red and itchy.

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

5. STORING ONDANSETRON 2MG/ML SOLUTION FOR INJECTION

Do not store above 25°C.

Keep the ampoule in the outer carton

Keep out of the reach and sight of children

Do not use after the expiry date stated on the label.

Chemical and physical in use stability has been demonstrated for 24 hours at 25°C and 5°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

For single use. Discard any unused product immediately after use.

This leaflet was prepared in July 2005

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2mg of ondansetron (as hydrochloride dihydrate)

Each 2ml ampoule contains 4mg of ondansetron (as hydrochloride dihydrate)

Each 4ml ampoule contains 8mg of ondansetron (as hydrochloride dihydrate)

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution, free from particles.

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 (PONV).

4.2. Posology and method of administration

For intravenous use or for intramuscular use. Refer to Section 6.6 'Instructions for Use and Handling', for information on compatibility with intravenous fluids and other drugs.

For single use. Discard any unused product immediately after use

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 50-100ml 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/m² 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 0.1mg/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 0.1mg/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 5HT₂ receptor antagonists. As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

This medicinal product contains less than 1mmol (23mg) of sodium in each ampoule. It is essentially 'sodium-free'.

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:- A04AAO 1 Serotonin (5HT₃) antagonist

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

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

5.2. Pharmacokinetic Properties

Following oral administration, 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 (85%) 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 ten 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 100ml/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at three years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

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

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

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

5.3. Preclinical safety data

No additional data of relevance.

PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Water for injections.

6.2. Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

6.3. Shelf life

Two years

After dilution, see section 6.4 Special precautions for storage.

6.4. Special precautions for storage

Do not store above 25°C.
Keep the ampoule in the outer carton
Keep out of the reach and sight of children

After dilution:-

Chemical and physical in use stability has been demonstrated for 24 hours at 25°C and 5°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5. Nature and contents of container

Ondansetron 2mg/ml Injection (4mg in 2ml) - Type I Ph Eur amber glass ampoules of 3ml capacity
Ondansetron 2mg/ml Injection (8mg in 4ml) - Type I Ph Eur amber glass ampoules of 4ml capacity

Each pack contains one, five or ten ampoules.

6.6. Instructions for use and handling

For single use. Discard any unused product immediately after use.

Ondansetron injection should not be autoclaved.

Compatibility with intravenous fluids:

Ondansetron injection should only be admixed with those infusion solutions which are recommended-

Sodium Chloride Intravenous Infusion BP 0.9%w/v
Glucose Intravenous Infusion BP 5%w/v
Mannitol Intravenous Infusion BP 10%w/v
Ringers Intravenous Infusion
Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP
Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

In keeping with good pharmaceutical practice dilutions of Ondansetron Injection in intravenous fluids should be prepared at the time of infusion, although chemical and physical in use stability after dilution has been demonstrated for 24 hours at 25°C and 5°C.

Compatibility with other drugs: Ondansetron may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively):

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil: Concentrations up to 0.8 mg/ml (e.g. 2.4g in 3 litres or 400mg in 500ml) administered at a rate of at least 20ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin: Concentrations in the range 0.18mg/ml to 9.9mg/ml (e.g. 90mg in 500ml to 990mg in 100ml), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72mg in 500ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5ml for 250mg and 10ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100mg to 1g, reconstituted with Water for Injections BP, 5ml per 100mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10-100mg reconstituted with Water for Injections BP, 5ml per 10mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over two to five minutes via the Y-site of an infusion set delivering 8 or 32mg of ondansetron diluted in 50-100ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 micrograms to 2.5mg/ml for dexamethasone sodium phosphate and 8 micrograms to 1mg/ml for ondansetron.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL13 9UF
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Ondansetron 2mg/ml Injection (4mg in 2ml) - PL 04543/0507
Ondansetron 2mg/ml Injection (8mg in 4ml) - PL 04543/0508

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st March 2006

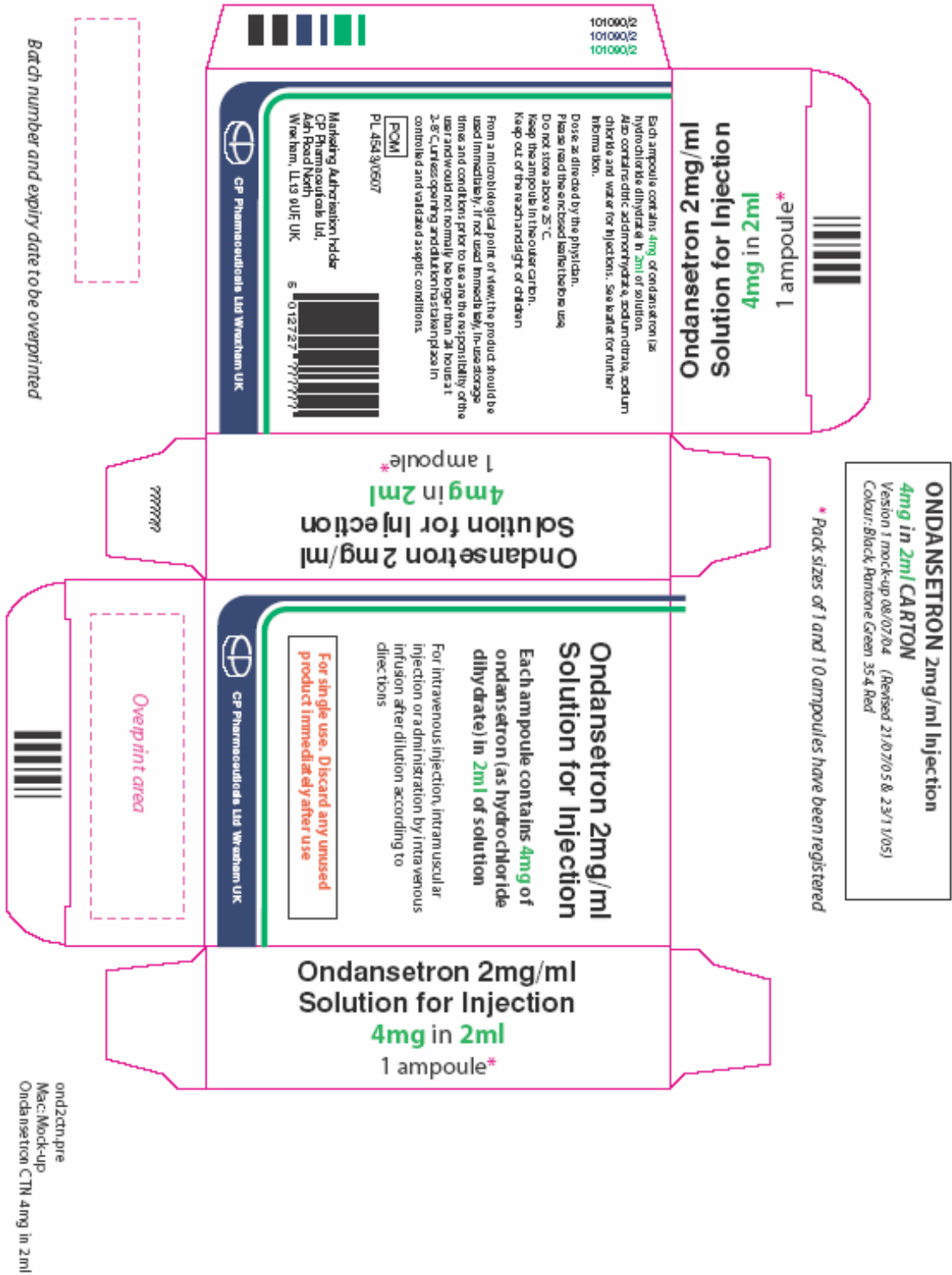
10. DATE OF REVISION OF THE TEXT

29th March 2006

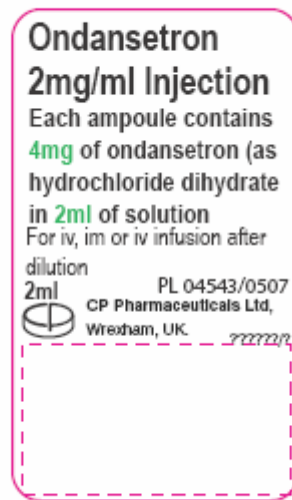
**ONDANSETRON 4MG/2ML INJECTION (ONDANSETRON HYDROCHLORIDE)
PL 04543/0507**

LABELLING

CARTON



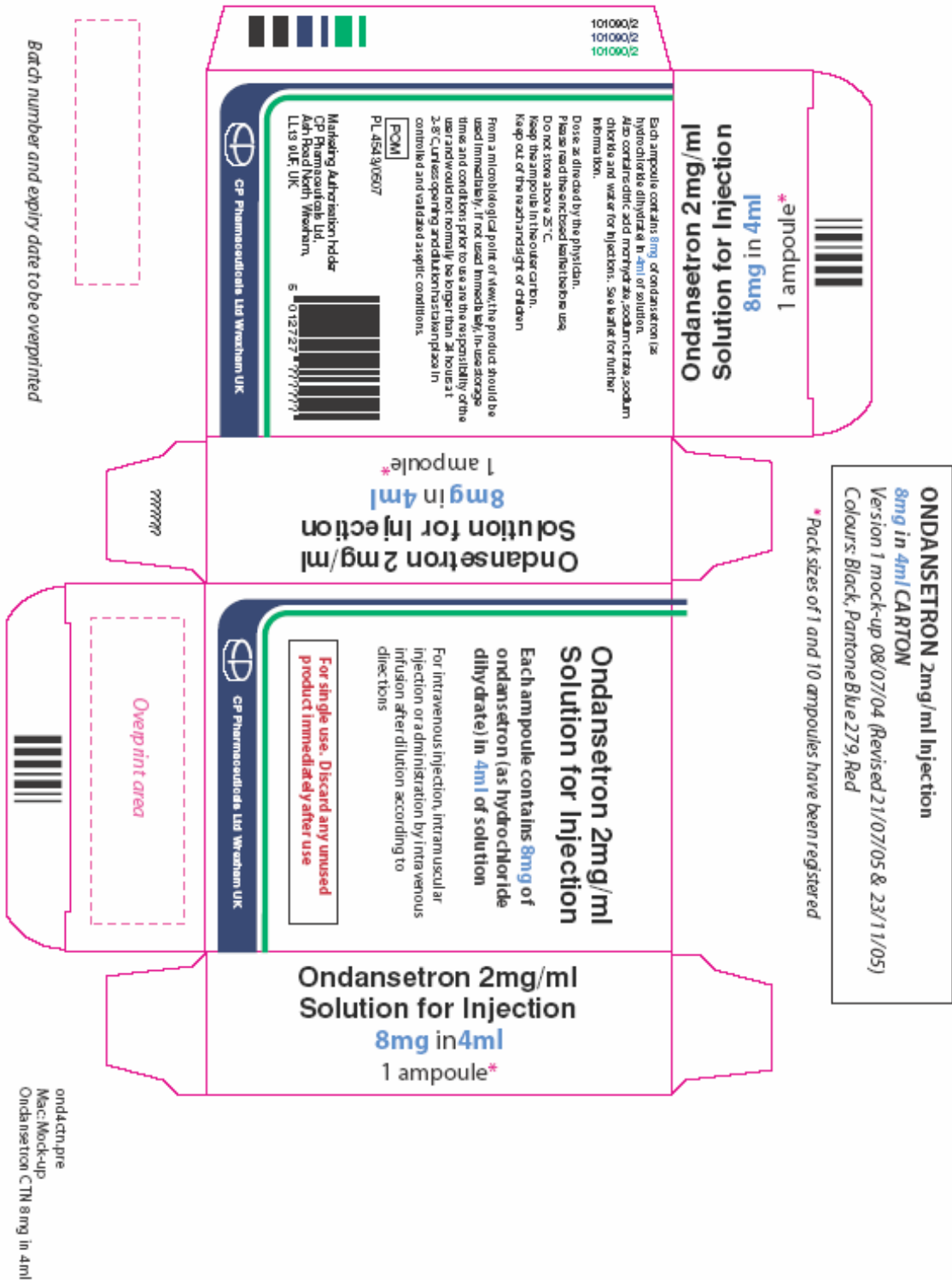
LABEL



**ONDANSETRON 8MG/4ML INJECTION (ONDANSETRON HYDROCHLORIDE)
PL 04543/0508**

LABELLING

CARTON



LABEL

