

**ONDANSETRON 2MG/ML INJECTION
(ONDANSETRON HYDROCHLORIDE)
PL 04515/0152**

UKPAR

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LAY SUMMARY

The MHRA granted Mayne Pharma Plc a Marketing Authorisation (licence) for the medicinal product Ondansetron 2mg/ml Injection (PL 04515/0152) on 15th June 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 Injection contains 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 Injection is equivalent to the approved product, Zofran Injection 2mg/ml. Ondansetron 2mg/ml Injection can therefore be used interchangeably with Zofran Injection 2mg/ml.

No new or unexpected safety concerns arose from this application. It was, therefore, judged that the benefits of taking Ondansetron 2mg/ml Injection outweigh the risks. Hence a Marketing Authorisation has 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 a marketing authorisation for the medicinal product Ondansetron 2mg/ml Injection (PL 04515/0152) to Mayne Pharma Plc on 15th June 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original product Zofran Injection 2mg/ml.

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

Ondansetron hydrochloride, a carbazole, is a selective inhibitor of type 3 serotonin (5-hydroxytryptamine) receptors (5-HT₃) that exhibits anti-emetic activity.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

This complex abridged application is for an isotonic solution for injection containing 2mg/ml (4mg/2ml and 8mg/4ml) of the serotonin (5HT₃) antagonist ondansetron (as hydrochloride dihydrate). The applicant has proposed that the product is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting. The product may be administered by IM and IV injection.

This application has been made under the first paragraph of Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EEC, claiming essential similarity to Zofran Injection 2mg/ml authorised to GlaxoSmithkline in Belgium in March 1990. The reference product authorised in the UK is Zofran Injection 2mg/ml (PL 00004/0375). This product was authorised to Glaxo Operations UK Ltd trading as GlaxoSmithkline UK on 7th March 1990.

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. ACTIVE 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.

3.2 MANUFACTURE

3.2.1 Manufacturing process description and process controls

A letter of access dated 29 August 2003 and the open part of the Drug Master File (DMF) have been provided for the named source. The Applicant's part is identical to the version registered with the MHRA. At the time of assessment, no products had been authorised in the UK using this source of active substance.

The synthetic route is adequately described in the DMF.

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 Elucidation of structure and other characteristics

This has been adequately described in the DMF.

3.3.2 Impurities

This has been adequately described in the DMF.

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.

The finished product manufacturer also tests batches of active substance for an additional impurity that was detected during photostability studies.

3.4 CONTROL OF ACTIVE SUBSTANCE

3.4.1 Specification

Ondansetron hydrochloride dihydrate is the subject of Ph Eur monograph. The substance is also described in the USP/NF. Batches of active substance are controlled to the stated specifications. The specifications satisfy the requirements of the Ph Eur monograph. All batches received by the finished product manufacturer are fully tested in accordance with the specifications.

The proposed limit for a residual solvent complies with ICH recommended limit.

The proposed limit for bacterial endotoxins is based on the USP drug product monograph. The limit complies with the Ph Eur requirement of NMT 350 EU/70kg based on a maximum dose of 32mg/day.

Differences between the limits applied by the manufacturers of the active substance and finished product arise as a result of the differences between the Ph Eur and USP monographs.

3.4.2 Analytical procedures / validation

The active substance manufacturer uses analytical methods described in the Ph Eur monograph supplemented with an in-house method for residual solvents and the USP method for organic volatile impurities.

The finished product manufacturer performs the compendial tests as well as tests for microbial quality, bacterial endotoxins and heavy metals. A separate method is used for determination of impurities E and H. In-house methods are used for assay and related substances.

The assay method has been validated in accordance with ICH.

The methods for related substances have been validated in accordance with ICH.

Residual solvent is determined by a method that has been validated in accordance

with ICH.

The microbial content and bacterial endotoxins methods have been validated.

3.4.3 Batch analyses

Satisfactory Certificates of Analysis have been provided for several batches of active substance manufactured by the proposed active substance manufacturer in March 2000..

3.4.4 Justification of specification

The applicant has provided a justification for the proposed specification.

3.5 REFERENCE STANDARDS OR MATERIALS

These have been described in the DMF. In addition, the finished product manufacturer has qualified a single batch of ondansetron hydrochloride dihydrate as an in-house reference standard. A satisfactory report and certificate of analysis have been provided on the characterisation of this batch.

3.6 CONTAINER CLOSURE SYSTEM

The active substance is packed in double polyethylene bags in fibre drums.

3.7 STABILITY

3.7.1 Stability summary and conclusions

Ondansetron shows some sensitivity to temperature and moisture and should be protected from light. Data have been provided for several batches manufactured in March 2000 that support a re-test period of 36 months.

Satisfactory stability data has been presented in the DMF.

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 up to 5 years and that an annual batch will be added to the programme.

4. MEDICINAL PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE MEDICINAL PRODUCT

Table 1: Qualitative composition of ingredients

Ingredient	Reference Standard
Ondansetron hydrochloride dihydrate	Ph Eur
Citric acid monohydrate	Ph Eur
Sodium citrate	Ph Eur
Sodium chloride	Ph Eur
Water for injections	Ph Eur
Nitrogen, pure grade	NF

4.2 PHARMACEUTICAL DEVELOPMENT

4.2.1 Components of the drug product

Composition of the proposed single dose product is based on the reference product. A satisfactory summary of product development has been provided.

Results of active substance - excipient compatibility studies have not been conducted on the basis that the same excipients used in the originator product are used. This is acceptable.

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.

Compatibility of the bulk solution with Silastic and Pharmed tubes over 4 hours has been demonstrated. Compatibility has also been shown with stainless steel and with the West V-35 4432/50 grey rubber stoppers.

Information on suitability of the filters used in the manufacturing process is discussed in section 4.3.5 of this report.

Samples of the proposed product and the UK originator product were stored inverted under accelerated ICH conditions. It was concluded that the products had similar impurity profiles and that the requirements of essential similarity are met with respect to impurities.

Sensitivity of the product in clear vials to UV light has been demonstrated. Use of amber glass overcame this problem. Confirmatory studies of the product in amber

vials under ICH conditions demonstrated the physical and chemical stability of the product.

Compatibility with infusion fluids has been studied on the basis of the recommendations for the originator product. The results confirm the stability of the product when stored at 2-8°C and 25°C in 0.9% sodium chloride, 5% glucose, Ringer's Solution, 10% mannitol, 0.3% potassium chloride/0.9% sodium chloride and in 0.3% potassium chloride/5% glucose.

4.2.3 Manufacturing process development

Satisfactory details of the development of the manufacturing process have been provided.

4.2.4 Container and closure system

2ml and 5ml amber Type I glass vials are used with rubber closures and aluminium caps. This pack is suitable.

4.3 MANUFACTURE

4.3.1 Manufacturer(s)

A valid Manufacturing Authorisation has been provided for the proposed site of manufacture.

Batch release is performed by Mayne Pharma plc, Queensway, Royal Leamington Spa, Warwickshire, UK under WI/4515/1. A copy of the current licence has been provided.

4.3.2 Batch formula

Satisfactory formulae have been provided for the manufacture of a stated 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.

4.3.4 Control of critical steps and intermediates

Critical steps have been identified and satisfactory controls stated.

4.3.5 Process validation and/or evaluation

It is stated that process validation will be performed on the first three production batches of each presentation. A copy of the process validation protocol has been provided.

To support use of the proposed filters, studies have been performed. No issues arise.

Sterilisation processes have been adequately validated.

Integrity of the container/closure has been demonstrated.

4.4 CONTROL OF EXCIPIENTS

4.4.1 Specifications

All ingredients are stated as complying with Ph Eur monographs.

Satisfactory specifications have been provided for all ingredients. All incoming batches will be fully tested against the specifications. Satisfactory supplier/finished product manufacturer Certificates of Analysis have been provided.

4.4.2 Excipients of human or animal origin

It is stated on the MAA forms that no materials of animal origin are contained in or used in the manufacture of this product. Satisfactory signed declarations have been provided.

No genetically modified organisms are included in this product.

4.5 CONTROL OF MEDICINAL PRODUCT

4.5.1 Specification

The proposed finished product specification has been described.

The specification meets the requirements of the USP monograph for Ondansetron Injection and the general requirements of the Ph Eur and ICH.

All known and unknown impurities are suitably controlled in the specification.

The limit for bacterial endotoxins is in accordance with the USP limit for Ondansetron Injection (9.9 IU/mg).

4.5.2 Analytical procedures / Validation of analytical procedures

In general the analytical methods are those described in the USP or Ph Eur.

In-house methods are used for assay and related substances. These methods are based on the methods used for analysis of the active substance, and have been validated in accordance with ICH.

The method for sterility has been validated and shown to be suitable for use with the product.

The method for bacterial endotoxins has been validated.

4.5.3 Batch analyses

Satisfactory Certificates of Analysis have been provided for batches manufactured at bulk batch sizes at the proposed commercial site in August 2002 and February 2003. All batches comply with the proposed release specification. It should be noted that bacterial endotoxins were tested using a different method than that proposed for batch release. Sufficient data have been provided.

4.5.4 Characterisation of impurities

A detailed discussion of the potential impurities has been provided.

4.5.5 Justification of specifications

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

4.6 REFERENCE STANDARDS OR MATERIALS

These have been adequately described in the DMF. In addition, the finished product manufacturer has qualified a single batch of ondansetron hydrochloride dihydrate as an in-house reference standard. A satisfactory report and certificate of analysis have been provided on the characterisation of this batch.

4.7 CONTAINER-CLOSURE SYSTEM

The product is presented in 2ml and 5ml capacity amber Type I glass vials with rubber closures and aluminium closures with plastic flip-off caps containing 2ml and 4ml solution, respectively. The vials are supplied in packs of 5 vials.

It is stated that the vials meet the requirements of the Ph Eur for Type I glass and for glass containers for pharmaceutical use. Satisfactory certificates of compliance (with Ph Eur) have been provided by the named vial supplier to support this supply of 2ml and 5ml vials, together with drawings, specifications and dimensional data.

The elastomeric closures comply with Type I requirements as described in the Ph Eur and with the monograph *Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders*. Confirmation has been provided by the finished product manufacturer that tests for description, identification and dimensions will be performed on receipt of each consignment.

The integrity of sealed vials has been shown for vials filled with tryptone Soya Broth (TSB) immersed in TSB inoculated with *Brevundimonas diminuta*.

Supplier's drawings of the vials and elastomer stoppers have been provided.

The first batch of vials received by the finished product manufacturer each year will be tested for conformance with the USP tests and to confirm sulphur treatment. Thereafter, each batch is released based on a satisfactory Certificate of Compliance and a positive residual acidity test to confirm sulphur treatment.

The first batch of stoppers received by the finished product manufacturer each year will be tested for conformance with the USP tests and to confirm absence of toxicity. Thereafter, each batch is released based on a satisfactory Certificate of Compliance.

Certificates of Conformance and Certificates of Analysis from the finished product manufacturer have been provided for batches of vials, stoppers and caps.

4.8 STABILITY

4.8.1 Stability summary and conclusion

Stability data have been provided for batches of 2ml fill and 4ml fill manufactured in January/February 2002 and provided in the proposed commercial container/closures. The batches were at least 10% of the proposed commercial batch size. Batches of vials were stored upright and inverted.

Analytical methods used were as described for routine batch release, except that a different method was used for endotoxin testing.

Stability data provided: 5°C, long term, intermediate and accelerated conditions

Test parameters: appearance, pH, assay, related substances, extractable volume, bacterial endotoxins, sterility, particulate matter

Only minor changes attributable to analytical variation were seen in samples stored under long term and accelerated conditions.

The applicant has proposed a shelf-life of 24 months for product with no specific storage temperatures. It is recommended in the SPC that the product is used immediately. However, an in-use shelf-life of 24 hours (after first opening or dilution) is permitted for product stored at 2-8°.

4.8.2 Post-approval stability protocol and stability commitment

The applicant has provided confirmation that stability studies will be conducted on the first three production batches for each presentation and thereafter a minimum of one batch will be added to the programme each year.

4.9 BIOEQUIVALENCE/BIOAVAILABILITY

Bioequivalence studies are not necessary to support this application.

5. MAA FORM

The MAA form is satisfactory.

6. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is satisfactory.

7. LABELLING

The labelling is satisfactory.

8. PATIENT INFORMATION LEAFLET

The leaflet is satisfactory.

9. STATEMENT ABOUT THE AUTHOR OF THE OVERALL QUALITY SUMMARY

A satisfactory *Curriculum Vitae* has been provided for the Pharmaceutical Expert, a Chartered Chemist.

10. CONCLUSIONS

A Marketing Authorisation may be granted.

The requirements of essential similarity are met with respect to qualitative and quantitative content of the active substance. Given the route of administration, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

PRECLINICAL ASSESSMENT

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

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.

This application is one national abridged MAA.

The application is submitted under the provisions of Article 10.1 [formerly Article 10.1 (a) (iii)] claiming that the product is ***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 an 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.

2. INDICATIONS

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

This is considered satisfactory and is consistent with the SmPC for Zofran 2 mg/ml injection, PL 00004/0375.

3. DOSE & DOSE SCHEDULE

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

This is considered satisfactory and is consistent with the 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 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 this MAA.

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 text for sections 4.3 to 5.3 of the proposed SmPC for this product has been compared with the Summary of Product Characteristics approved for Zofran in the UK in September 2004.

This is satisfactory and is consistent with the SmPC for Zofran 2 mg/ml injection, PL 00004/0375.

10. PATIENT INFORMATION LEAFLET

The proposed PIL has been compared with the Zofran 2mg/ml PIL.

The proposed PIL is considered satisfactory and is fully consistent with the SmPC for the proposed product and the PIL for Zofran 2 mg/ml injection, PL 00004/0375 approved in the UK in September 2004.

11. LABELLING

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

12. CONCLUSIONS

Overall there is no clinical objection to the grant of MA for this application. No new or unexpected safety concerns arise from this application. The proposed SmPC is considered satisfactory. The proposed PIL is consistent with the proposed SmPC and the 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

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

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 this application.

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 product and the innovator product 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 05/06/2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 03/12/2003.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 03/12/2004, 15/12/2004, 18/01/2005, 02/02/2005 and 17/05/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 18/01/2005, 28/01/2005, 01/03/2005 and 17/05/2006.
5	The application was determined on 15/06/2006.

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**ONDANSETRON 2MG/ML INJECTION
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution contains 2 mg ondansetron as ondansetron hydrochloride dihydrate.

Each vial with 2 ml of solution contains 4 mg of ondansetron in Water for Injections.

Each vial with 4 ml of solution contains 8 mg of ondansetron in Water for Injections.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection (Injection)

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

4.2. Posology and method of administration

Ondansetron Injection can be given either by intravenous or intramuscular administration only. Other preparations are available for oral or rectal administration.

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING:

Adults:

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

Emetogenic chemotherapy and radiotherapy:

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron Injection 8 mg 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 should be continued for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy:

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, Ondansetron Injection has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

A single dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy.

A dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

A single dose of 32 mg diluted in 50-100 ml 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. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment.

Children:

Ondansetron Injection may be administered as a single intravenous dose of 5 mg/m² immediately before chemotherapy, followed by 4 mg orally twelve hours later. 4 mg orally twice daily should be continued for up to 5 days after a course of treatment.

Elderly:

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Patients with renal impairment:

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

Patients with hepatic impairment:

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

POST OPERATIVE NAUSEA AND VOMITING:

Adults:

For the prevention of post operative nausea and vomiting: Ondansetron Injection may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established post operative nausea and vomiting: a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over):

For prevention of post operative nausea and vomiting in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For treatment of established post operative nausea and vomiting in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There is limited data on the use of Ondansetron Injection in the prevention and treatment of post operative nausea and vomiting in children under 2 years of age.

Elderly:

There is limited experience in the use of ondansetron in the prevention and treatment of post operative nausea and vomiting in the elderly, however ondansetron 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 is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism:

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give 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 ondansetron or to any of the excipients.

4.4. Special warning and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃ receptor antagonists.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per 2 mg/ml, i.e. 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 and propofol.

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

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

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

4.6. Pregnancy and lactation

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

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

4.7. Effects on ability to drive and use machines

Ondansetron Injection has no influence on the ability to drive and use machines.

4.8. Undesirable effects

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

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

Immune system disorders:

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders:

Very common: Headache.

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

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

Eye disorders;

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

Very rare: Transient blindness predominantly during intravenous administration

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

Cardiac disorders:

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

Vascular disorders:

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders:

Uncommon: Hiccups.

Gastrointestinal disorders:

Common: Constipation.

Hepatobiliary disorders:

Uncommon: Asymptomatic increases in liver function tests*.

*These events were observed commonly in patients receiving chemotherapy with cisplatin.

General disorders and administration site conditions:

Common: Local intravenous injection site reactions.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antiemetics and antinauseants, serotonin (5-HT₃) antagonists, ATC code: A04A A01

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

Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT₃ receptors on 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

Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

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

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

Ondansetron is moderately highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine

polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

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

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

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 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

citric acid monohydrate
sodium citrate
sodium chloride
Water for Injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale: 2 years

After first opening of the container: 24 hours (see section 6.4)

6.4 Special precautions for storage

As packaged for sale: The medicinal product does not require any special storage conditions. Keep vial in the outer carton.

After first opening of the container:

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°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 normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

2 ml type 1 amber glass vials containing 2 ml of solution, with rubber closures and aluminium caps.

5 ml type 1 amber glass vials containing 4 ml of solution, with rubber closures and aluminium caps.

Presented in packs of 5.

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

Compatibility with intravenous fluids

Ondansetron Injection should only be admixed with those infusion solutions which are recommended:

Sodium Chloride Intravenous Infusion 0.9% w/v

Glucose Intravenous Infusion 5% w/v

Mannitol Intravenous Infusion 10% w/v

Ringers Intravenous Infusion

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

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

Compatibility with other drugs

Ondansetron Injection 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 20 ml 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 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml 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. 2.5 ml for 250 mg and 10 ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100 mg to 1g, reconstituted with Water for Injections BP, 5 ml per 100 mg 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, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

7. MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW

8. MARKETING AUTHORISATION NUMBER

PL 04515/0152

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2006

10 DATE OF REVISION OF THE TEXT

15/06/2006

**ONDANSETRON 2MG/ML INJECTION
(ONDANSETRON HYDROCHLORIDE)
PL 04515/0152**

PRODUCT INFORMATION LEAFLET



TECHNICAL LEAFLET

Ondansetron 2 mg/ml Injection

This is an extract from the Summary of Product Characteristics to assist in the administration of Ondansetron Injection. You should however be familiar with the full SmPC.

For Intravenous and Intramuscular Injection, Intravenous Infusion

Incompatibilities

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

Ondansetron Injection should only be admixed with those infusion solutions that are recommended (see Preparation Instructions).

Preparation Instructions

Ondansetron Injection should only be admixed with those infusion solutions that are recommended:

Sodium Chloride Intravenous Infusion 0.9% w/v

Glucose Intravenous Infusion 5% w/v

Mannitol Intravenous Infusion 10% w/v

Ringers Intravenous Infusion

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

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

Compatibility with other drugs

Ondansetron may be administered by intravenous infusion at 1 mg/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 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. 2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml 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 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml 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. 2.5 ml for 250 mg and 10 ml for 2 g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

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

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

Dosage and Administration

Ondansetron Injection can be given either by intravenous or intramuscular administration only. Other preparations are available for oral or rectal administration.

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING:

Adults:

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

Emetogenic chemotherapy and radiotherapy:

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron Injection 8 mg 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 should be continued for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy:

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, Ondansetron Injection has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

A single dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy.

A dose of 8 mg by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

A single dose of 32 mg diluted in 50-100 ml of saline or other compatible infusion fluid 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. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment.

PATIENT INFORMATION LEAFLET

This leaflet contains important information about your medicine; read it carefully.

Keep this leaflet; you may want to read it again.

If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Ondansetron 2 mg/ml Injection

- The active substance is ondansetron
- The other ingredients are citric acid monohydrate, sodium citrate, sodium chloride and Water for Injections.

This medicinal product contains less than 1 mmol sodium (23 mg) per 2 mg/ml, i.e. essentially "sodium free".

The marketing authorisation holder and company responsible for batch release in the EU is Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, United Kingdom.

The manufacturer is Mayne Pharma Limited, 1 Lexia Place, Mulgrave, Australia, 3170.

1. What Ondansetron Injection is and what it is used for

Ondansetron Injection is an anti-sickness medicine in the form of a solution for injection.

Each millilitre (ml) of solution contains 2 milligram (mg) of ondansetron as ondansetron hydrochloride dihydrate. It is presented in glass containers called vials. The vials containing 2 ml of solution contain 4 mg of ondansetron and the vials containing 4 ml of solution contain 8 mg of ondansetron. It is available in packs of 5 x 2 ml or 5 x 5 ml vials.

Ondansetron is used to help to stop you from feeling sick or being sick after treatment with cancer medicines, radiotherapy or after an operation.

2. Before Ondansetron Injection is used

Ondansetron Injection should not be used:

- if you have shown signs of hypersensitivity (severe allergy) to this or a similar medicine on previous occasions
- if you are pregnant or think you may be pregnant
- if you are breastfeeding

Special care will be taken:

- if you have a blockage in your gut or suffer from severe constipation
- if your liver is not working as well as it should
- with children less than 2 years of age

Please tell your doctor if you are taking, or have recently taken, any other medicines, including ones that are not prescribed for you.

Do not drive or use machines:

- if you experience any effect which may lessen your ability to drive or use machines

3. How Ondansetron Injection is used

The dose of medicine given to you will depend on your age, medical condition and how well your liver is working.

This medicine will only be given into a muscle or vein. If it is given into a vein, it can either be given as an injection or via a drip (infusion).

If you are taking ondansetron to help relieve sickness while you are receiving anti-cancer medicines or radiotherapy:

Adults: you will be given 8 mg as slow injection either into the vein or into a muscle, immediately before you have your cancer treatment, followed by 8 mg orally every twelve hours. You will also receive ondansetron orally or by rectal administration for up to 5 days following your cancer treatment.

If the anti-cancer treatments you are receiving will make you feel very sick you may receive one of the following doses:

- A single slow injection of 8 mg of ondansetron either into a vein or a muscle immediately before your cancer treatment.
- A slow injection of 8 mg of ondansetron either into a vein or a muscle immediately before your anti-cancer treatment. This will be followed by two further injections of 8 mg of ondansetron, either into a vein or into a muscle,

4 8 1 8 4 8

Children:

Ondansetron Injection may be administered as a single intravenous dose of 5 mg/m² immediately before chemotherapy, followed by 4 mg orally twelve hours later. 4 mg orally twice daily should be continued for up to 5 days after a course of treatment.

Elderly:

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Patients with renal impairment:

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

Patients with hepatic impairment:

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

POST OPERATIVE NAUSEA AND VOMITING:**Adults:**

For the prevention of post operative nausea and vomiting: Ondansetron Injection may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established post operative nausea and vomiting: a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Children (aged 2 years and over):

For prevention of post operative nausea and vomiting in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For treatment of established post operative nausea and vomiting in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There is limited data on the use of Ondansetron Injection in the prevention and treatment of post operative nausea and vomiting in children under 2 years of age.

Elderly:

There is limited experience in the use of ondansetron in the prevention and treatment of post operative nausea and vomiting in the elderly, however ondansetron 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 is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism:

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

Warnings

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃ receptor antagonists.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per 2 mg/ml, i.e. essentially "sodium-free."

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.

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

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.

Storage

As packaged for sale: The medicinal product does not require any special storage conditions. Keep vial in the outer carton, in order to protect from light. Do not use if the vial is damaged or if the product contains particles or is cloudy.

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°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 normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Marketing Authorisation Holder

Mayne Pharma Plc
Warwickshire, CV31 3RW
United Kingdom

Date of Preparation

February 2006

Please tear here

Please tear here

two to four hours apart, or 1 mg per hour as an injection via a drip for up to 24 hours.

- A single dose of 32 mg of ondansetron diluted in saline, or another compatible solution, given as an injection via a drip over not less than 15 minutes immediately before your anti-cancer treatment.

You may also receive ondansetron orally or by rectal administration for up to 5 days after your anti-cancer treatment.

Children: you may receive a single injection into a vein immediately before your anti-cancer medicine, followed by 4 mg orally twelve hours later. This might be followed by oral administration for up to 5 days after your anti-cancer treatment.

If your liver is not working very well you will only receive a maximum dose of ondansetron of 8 mg per day.

If you are receiving ondansetron to help prevent or treat sickness after an operation:

Adults: you may be given 4 mg of ondansetron as a single injection into a muscle or as a slow injection into a vein at the same time that you are given your anaesthetic, or if you are feeling sick after your operation.

Children (aged 2 years and over): you may be given up to a maximum of 4 mg of ondansetron based on your body surface area by a slow injection into your vein, either before or after you are given your anaesthetic, or if you feel sick after your operation.

If your liver is not working very well you will only receive a maximum dose of ondansetron of 8 mg per day.

As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much, however, tell your doctor or nurse if you have any concerns.

4. Possible Side Effects

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

A few people can be allergic to some medicines; if any of the following rare side effects occur soon after having your injection, tell your doctor immediately:

- Sudden chest tightness or wheeziness
- Swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing)
- Skin rash - red spots or hives (skin lumps)
- Feeling faint

Very common (occurs in more than 1 of 10 users):

Headache

Common (occurs in more than 1 of 100 but less than 1 of 10 users):

Feeling of flushing and warmth, constipation, irritation and redness at the site of injection.

Uncommon (occurs in more than 1 of 1,000 but less than 1 of 100 users):

fits, abnormal muscle stiffness, body movements or shaking, chest pain, slow or irregular heartbeat, low blood pressure, hiccups.

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

Rare (occurs in more than 1 of 10,000 but less than 1 of 1,000 users):

Dizziness or light-headed feeling at the time of receiving the injection, blurring of vision.

Very rare (occurs in less than 1 of 10,000 users):

Temporary blindness whilst receiving the injection (does not usually last for more than 20 minutes).

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. Storing Ondansetron Hydrochloride Injection

Keep out of the reach and sight of children.

The medicinal product does not require any special storage instructions.

The vials should be kept in the outer carton to protect from light.

This medicine should not be used after the expiry date printed on the label and carton.

Date of Preparation

May 2006

481848

**ONDANSETRON 2MG/ML INJECTION
(ONDANSETRON HYDROCHLORIDE)
PL 04515/0152**

LABELLING – 2ML VIAL SIZE

CARTON



VIAL



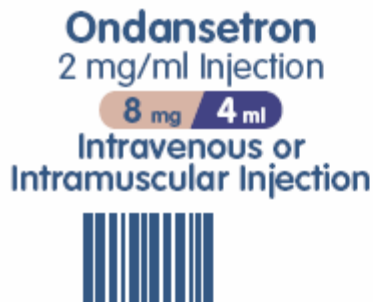
**ONDANSETRON 2MG/ML INJECTION
(ONDANSETRON HYDROCHLORIDE)
PL 04515/0152**

LABELLING – 4ML VIAL SIZE

CARTON



VIAL



PL 04515/0152
Mayne Pharma Plc

Q10020