

**ONDANSETRON 2MG/ML SOLUTION FOR INJECTION
(ONDANSETRON HYDROCHLORIDE DIHYDRATE)**

PL 24610/0003

UKPAR

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**ONDANSETRON 2MG/ML SOLUTION FOR INJECTION
(ONDANSETRON HYDROCHLORIDE DIHYDRATE)****PL 24610/0003****LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bowmed Limited a Marketing Authorisation (licence) for the medicinal product Ondansetron 2mg/ml solution for injection (PL 24610/0003) on 30th November 2007. This is a prescription-only medicine (POM) used to prevent you from feeling or being sick after medical or surgical treatment.

Ondansetron 2mg/ml solution for injection contains the active ingredient ondansetron (as ondansetron hydrochloride dihydrate), which belongs to a group of medicines called anti-emetics (anti-sickness medicines). Ondansetron is used to prevent you from feeling or being sick after medical or surgical treatment. It is often given before and after chemotherapy or radiotherapy.

The proposed product was considered to be a generic version of the reference product Zofran Injection 2mg/ml (PL 00004/0375, Glaxo Operations UK Ltd trading as GlaxoSmithkline).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Ondansetron 2mg/ml solution for injection outweigh the risk, hence a Marketing Authorisation has been granted.

**ONDANSETRON 2MG/ML SOLUTION FOR INJECTION
(ONDANSETRON HYDROCHLORIDE DIHYDRATE)**

PL 24610/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Bowmed Limited a Marketing Authorisation for the medicinal product Ondansetron 2mg/ml solution for injection (PL 24610/0003) on 30th November 2007. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged, standard application, according to Article 10.1 (a) (iii) first paragraph (now article 10(1)) of Directive 2001/83/EC, as amended. The application refers to the innovator product, Zofran Injection 2mg/ml (PL 00004/0375). This product was authorised to Glaxo Operations UK Ltd trading as GlaxoSmithkline UK on 7th March 1990.

The product is an isotonic solution for injection containing 2mg/ml (4mg/2ml and 8mg/4ml) of the serotonin (5HT₃) antagonist ondansetron (as hydrochloride dihydrate). It 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). The product may be administered by IM and IV injection

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

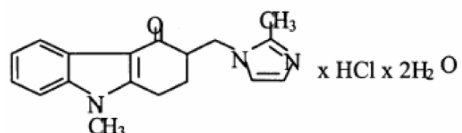
Ondansetron hydrochloride dihydrate

Nomenclature:

INN: Ondansetron hydrochloride dihydrate

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

Structure:



Molecular formula: C₁₈H₁₉N₃O.HCl.2H₂O

Molecular weight: 365.87

CAS No: 103639-04-9

Physical form: A white or almost white powder

Solubility: Sparingly soluble in water and in alcohol, soluble in methanol, slightly soluble in methylene chloride

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

An appropriate active substance specification has been provided based on the European Pharmacopoeia monograph, and in line with the Certificate of Suitability.

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

The manufacture and quality of active substance manufactured by the active substance manufacturer is controlled by a Certificate of Suitability.

Active ondansetron hydrochloride dihydrate is stored in appropriate packaging. It is packed in sealed polyethylene bags inside a laminated aluminium bag and placed into a tight and light resistant container. Specifications and Certificates of Analysis have been provided. The polyethylene bags in direct contact with the drug substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

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

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 60 months, when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium citrate, sodium chloride, citric acid monohydrate, and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

There are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles

Impurity profiles for the drug product were found to be similar to those for the reference product, and all the impurities are within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is based on the European Pharmacopeia and the USP monograph for 'Ondansetron injection', and is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is presented in 2ml and 4ml capacity amber-coloured or colourless Type I glass ampoules containing 2ml and 4ml solution, respectively. The ampoules satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral and ophthalmic preparations. Ampoules are supplied in packs of 5 in a plastic tray. For the colourless ampoules, an aluminium foil wrapping the plastic tray is provided. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. The tray with ampoules is packaged with the PIL and technical leaflet into a cardboard outer carton.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. The shelf life after reconstitution is 24 hours at a temperature of 2-8°C. The storage instruction is “Keep ampoule in outer carton”.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

EXPERT REPORT

The quality overview is written by an appropriately qualified expert and is satisfactory. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

PRODUCT INFORMATION:**Summary of Product Characteristics**

The updated, approved SPC is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the final SPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

Conclusion

The proposed product has been shown to be a generic version of the reference product, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 (a) (iii) first paragraph (now article 10(1)) of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Ondansetron 2mg/ml Solution for 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 (PONV).

CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application.

EFFICACY

No new data are submitted and none are required for this type of application.

SAFETY

No new data are submitted and none are required for this type of application.

EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory. A satisfactory Curriculum Vitae has been provided for the clinical expert.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Zofran Injection 2mg/ml (PL 00004/0375), are considered adequate. The product literature is approved.

The grant of a marketing authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 2mg/ml Solution for 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 were submitted and none are required for an application of this type.

EFFICACY

The applicant's Ondansetron 2mg/ml Solution for Injection has been demonstrated to be a generic version of the reference product Zofran Injection 2mg/ml (PL 00004/0375).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory and consistent with that for Zofran Injection 2mg/ml.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ondansetron hydrochloride dihydrate is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

**ONDANSETRON 2MG/ML SOLUTION FOR INJECTION
(ONDANSETRON HYDROCHLORIDE DIHYDRATE)**

PL 24610/0003

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 12th September 2005
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 19th October 2005
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 19th May 2006
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 17th August 2006
- 5 Following assessment of the response the MHRA requested further information relating to the quality dossier on 16th February 2007
- 6 The applicant responded to the MHRA's request, providing further information for the quality sections on 6th June 2007
- 7 The application was determined on 30th November 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Ondansetron 2mg/ml Solution for Injection is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 2mg/ml ondansetron (as hydrochloride dihydrate) in aqueous solution.

Each 2ml ampoule contains 4mg ondansetron hydrochloride dihydrate.

Each 4ml ampoule contains 8mg ondansetron hydrochloride dihydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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:

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

Emetogenic chemotherapy and radiotherapy: Ondansetron Injection can be given either by intravenous or intramuscular administration.

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 8mg 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 can be given either by intravenous or intramuscular administration. 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 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 Injection 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 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 5mg/m² immediately before chemotherapy, followed by 4mg orally twelve hours later.

4mg orally twice daily should be continued for up to 5 days after a course of treatment.

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

Patients with Renal Impairment:

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

Patients with hepatic Impairment:

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

Post-operative nausea and vomiting (PONV):

Adults: For the prevention of PONV, Ondansetron Injection can be administered by intravenous or intramuscular injection.

Ondansetron Injection 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 Injection in the prevention and treatment of PONV in children under 2 years of age.

Elderly: There is limited experience in the use of Ondansetron Injection in the prevention and treatment of PONV in the elderly; however Ondansetron Injection is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment: No alteration of daily dosage or frequency of dosing, or route of administration are required.

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

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

4.3 CONTRAINDICATIONS

Hypersensitivity to ondansetron or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

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

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

4.6 PREGNANCY AND LACTATION

Pregnancy:

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.

Lactation:

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron Injection 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 ($\geq 1/100$ and $<1/10$), uncommon ($\geq 1/1000$ and $<1/100$), rare ($\geq 1/10,000$ and $<1/1000$) and very rare ($<1/10,000$) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

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

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

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

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

Eye disorders

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

Very rare: Transient blindness predominantly during intravenous administration

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

Cardiac disorders

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

Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

Gastrointestinal disorders

Common: Constipation.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests#.

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

General disorders and administration site conditions

Common: Local i.v. 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: Serotonin (5HT₃) antagonist.

ATC code: A04A A01

Ondansetron is a potent, highly selective 5HT₃receptor-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 5HT₃receptors. 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 5HT₃receptors 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 (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 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 the pharmacokinetics of ondansetron. 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 300 mL/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 (0.1 mg/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 the pharmacokinetics of ondansetron to be essentially unchanged following IV administration.

Following intravenous or intramuscular dosing in patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32h).

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

36 months (unopened)

24 hours (dilutions stored at 2-8°C)

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Keep ampoule in the outer carton

6.5 NATURE AND CONTENTS OF CONTAINER

Type I clear or amber glass, 2ml and 4ml ampoules.

Five ampoules are packed in a plastic tray inside an outer carton.

When clear glass ampoules are used, trays are sealed in aluminium foil.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

Dilutions of ondansetron injection in Glucose Intravenous Infusion BP 5% w/v and Mannitol Intravenous Infusion BP 10% w/v have been demonstrated to be stable in polyvinyl chloride infusion bags. Dilutions of Ondansetron injection in the following intravenous fluids have been shown to be stable in polyethylene infusion bags: Mannitol Intravenous Infusion BP 10% w/v, Ringers Intravenous Infusion, Potassium Chloride 0.3% w/v and Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2-8°C unless reconstitution has taken place in controlled and validated aseptic conditions.

Compatibility with other drugs: Ondansetron Injection 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 Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8mg/50 ml respectively):

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240mg 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. 90mg in 500 ml to 990mg 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. 72mg in 500ml to 250mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250mg to 2000mg reconstituted with Water for Injections 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 5 minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over 2-5 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 microgram to 2.5mg/ml for dexamethasone sodium phosphate and 8 microgram to 1mg/ml for ondansetron.

7 MARKETING AUTHORISATION HOLDER

Bowmed Limited
113 Promenade
Cheltenham
GL50 1NW

8 MARKETING AUTHORISATION NUMBER(S)

PL 24610/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/11/2007

10 DATE OF REVISION OF THE TEXT

30/11/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Ondansetron 2 mg/ml Solution for Injection

(Ondansetron hydrochloride dihydrate)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do NOT pass it on to others. It may harm them even if their symptoms are the same as yours.
- 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.

In this leaflet:

1. What Ondansetron Injection is and what it is used for
2. Before you are given Ondansetron Injection
3. How Ondansetron Injection is given
4. Possible side effects
5. How to store Ondansetron Injection
6. Further information

The name of your medicine is Ondansetron 2mg/ml Solution for Injection (referred to as Ondansetron or Ondansetron Injection throughout this leaflet).

1. WHAT ONDANSETRON INJECTION IS AND WHAT IT IS USED FOR

This medicine contains the active substance Ondansetron (as Ondansetron hydrochloride dihydrate). The other ingredients are listed in section 6, Further Information.

Ondansetron is one of a group of medicines called anti-emetics (anti-sickness medicines). Your doctor has decided to give you ondansetron to prevent you from feeling or being sick after medical or surgical treatment. Ondansetron is often given before and after chemotherapy or radiotherapy.

2. BEFORE YOU ARE GIVEN ONDANSETRON INJECTION

You should not be given this medicine:

- If you are allergic or had any reactions to ondansetron or to any of the other ingredients in the injection (these are listed in Section 6, Further information).

Before you are given Ondansetron Injection you should tell your doctor:

- If you have a blockage in your gut or suffer from severe constipation
- If you have a problem with your liver.

Taking other medicines

You should tell your doctor if you are taking any of the following medicines as their effect may be changed or they may affect how well Ondansetron injection works:

- phenytoin (used for heart rhythm problems or seizures, e.g., epilepsy)
- rifampicin (an antibiotic used to treat infections such as tuberculosis)
- carbamazepine (used to prevent seizures)
- tramadol (a painkiller).

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines including medicines obtained without a prescription.

Children:

For children having chemotherapy and/or radiotherapy that causes nausea and vomiting:

The dose depends on your child's weight and height, and is given by intravenous injection immediately before chemotherapy followed by a 4mg tablet 12 hours later. Your child may then be given a 4mg tablet twice a day for up to 5 days following chemotherapy.

For children (aged two years and over) suffering from nausea and vomiting following an operation:

The dose depends on your child's weight and is given by intravenous injection. The usual dose is 0.1mg/kg up to a maximum of 4mg.

The injection may be given before the child is given an anaesthetic.

4. POSSIBLE SIDE EFFECTS

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

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face, lips or throat, rash or itching (especially affecting your whole body) should be reported to a doctor immediately.

The following side effects have also been reported:

Very common side effects (probably affecting more than 1 in 10 people)

- Headache.

Common side effects (probably affecting fewer than 1 in 10 people)

- Constipation
- Feeling of warmth or flushing of the face
- Irritation and redness at the site of injection.

Uncommon side effects (probably affecting fewer

Pregnancy and breast-feeding

If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before you are given this medicine.

Driving and using machines

Ondansetron is not expected to have an effect on you driving or using machines.

3. HOW ONDANSETRON INJECTION IS GIVEN
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The injection will usually be given by a doctor or nurse. It should start to work soon after having the injection. If you continue to be sick or feel sick, tell the doctor or nurse.

Adults and the elderly:

For patients having chemotherapy and/or radiotherapy that causes nausea (feeling sick) and vomiting (being sick): The recommended dose is 8mg given by intravenous injection (into a vein) or intramuscular injection (into a muscle), immediately before chemotherapy or radiotherapy. Afterwards you may be given ondansetron as a tablet or syrup every 12 hours.

For patients receiving chemotherapy that causes severe nausea and vomiting:

Ondansetron Injection can be given in any of the following 3 ways:

1. A single dose of 8mg by slow intravenous or intramuscular injection immediately before chemotherapy or
2. 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 (through an intravenous drip) of 1mg/hour for up to 24 hours or
3. A single dose of 32 mg diluted in 50-100 ml of an infusion liquid, and infused through an intravenous drip over 15 minutes immediately before chemotherapy.

Afterwards you may be given ondansetron as a tablet or syrup every 12 hours. The dose and way that Ondansetron is given depends on how likely the chemotherapy is to make you sick.

For patients suffering from nausea and vomiting following an operation:

The recommended dose is 4mg given by intramuscular or intravenous injection. The injection will usually be given just before you are given an anaesthetic.

Patients with moderate or severe liver disease:

The total daily dose given in these patients is 8 mg.

than 1 in 100 people):

- Seizures ("Fits")
- Abnormal body movements or shaking
- Upward movement of the eyes
- Slow or irregular heartbeat
- Chest pain
- Low blood pressure (hypotension)
- Hiccups
- Changes in blood tests to check how your liver is working (commonly seen in patients receiving chemotherapy with cisplatin).

Rare side effects (probably affecting fewer than 1 in 1,000 people)

- Visual disturbances e.g. blurred vision (mainly during rapid injection into a vein)
- Muscle cramps
- Dizziness (during rapid injection into a vein).

Very rare side effects (probably affecting fewer than 1 in 10,000 people)

- Temporary blindness (mainly during injection into a vein and in patients receiving chemotherapy e.g. cisplatin).

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

5. HOW TO STORE ONDANSETRON INJECTION
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Keep out of the sight and reach of children.

Keep the ampoule in the outer carton.

Your doctor, pharmacist or nurse will know how to store Ondansetron Injection properly.

Do not use Ondansetron injection after the expiry date which is stated on the label.

6. FURTHER INFORMATION

What Ondansetron Injection contains:

- The active ingredient is Ondansetron hydrochloride dihydrate 2mg/ml
- The other ingredients are citric acid monohydrate, sodium citrate, sodium chloride, and water for injections.

What Ondansetron Injection looks like and contents of the pack:

Ondansetron injection is a colourless solution in a clear or amber glass ampoule. Five ampoules are supplied in a carton. The clear glass ampoules are also wrapped in aluminium foil.

Each 2ml ampoule contains 4mg Ondansetron.

Each 4ml ampoule contains 8mg Ondansetron.

Marketing Authorisation Holder:

Bowmed Limited, 113 Promenade, Cheltenham, UK

Manufacturer:

Sofarimex Industria Quimica e Farmaceutica Lda, Cacem, Portugal

MEDICAL INFORMATION LEAFLET

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only.

Compatibility with infusion fluids:

Ondansetron Injection may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or syringe pump.

Ondansetron injection should only be admixed with those infusion solutions that 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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2-8°C unless reconstitution has taken place in controlled and validated aseptic conditions.

Storing Ondansetron Injection:

Keep the ampoules in the outer carton.
Ondansetron Injection should not be autoclaved.

Posology and method of administration

Chemotherapy and radiotherapy:

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

Emetogenic chemotherapy and radiotherapy:

Ondansetron Injection can be given either by intravenous or intramuscular administration.

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

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

Patients with Renal Impairment:

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

Patients with hepatic Impairment:

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

Post-operative nausea and vomiting (PONV):

Adults: For the prevention of PONV, Ondansetron Injection can be administered by intravenous or intramuscular injection.

Ondansetron Injection 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 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 8mg 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 can be given either by intravenous or intramuscular administration. 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 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 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 Injection 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 should be continued for up to 5 days after a course of treatment.

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 Injection in the prevention and treatment of PONV in children under 2 years of age.

Elderly: There is limited experience in the use of Ondansetron Injection in the prevention and treatment of PONV in the elderly; however Ondansetron Injection is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment:

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

Patients with hepatic impairment:

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

Patients with poor sparteine/debrisoquine metabolism:

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

This leaflet was last approved in xxxx.

LABELLING

Carton – 4mg in 2ml



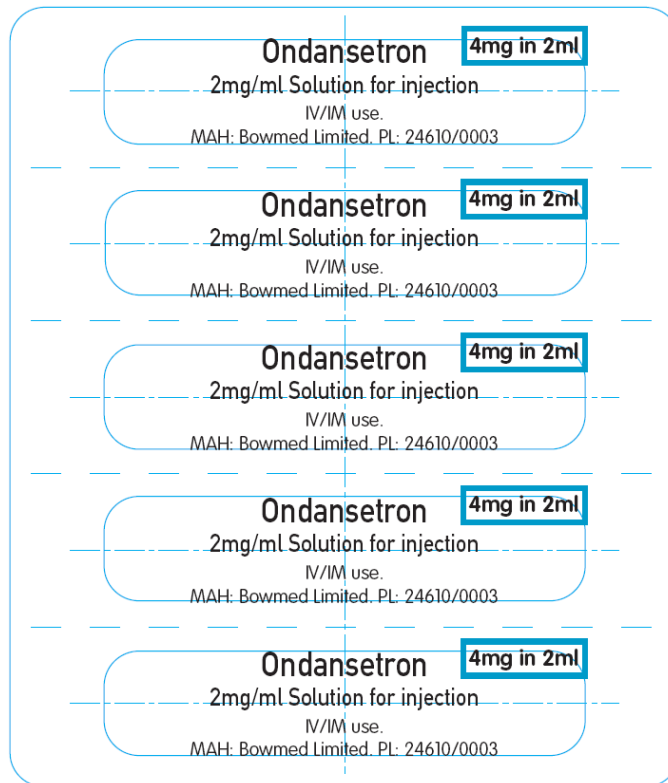
Braille - 4mg in 2ml

Braille text reads as follows (# represents "number sign"):



o n d a n s e t r o n
2 m g / m l
s o l u t i o n
f o r i n j e c t i o n

Foil - 4mg in 2ml



Ondansetron **4mg in 2ml**
2mg/ml Solution for injection
IV/IM use.
MAH: Bowmed Limited. PL: 24610/0003

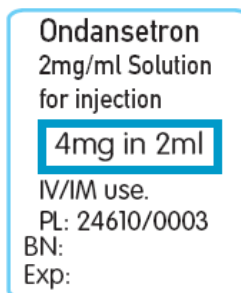
Ondansetron **4mg in 2ml**
2mg/ml Solution for injection
IV/IM use.
MAH: Bowmed Limited. PL: 24610/0003

Ondansetron **4mg in 2ml**
2mg/ml Solution for injection
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2mg/ml Solution for injection
IV/IM use.
MAH: Bowmed Limited. PL: 24610/0003

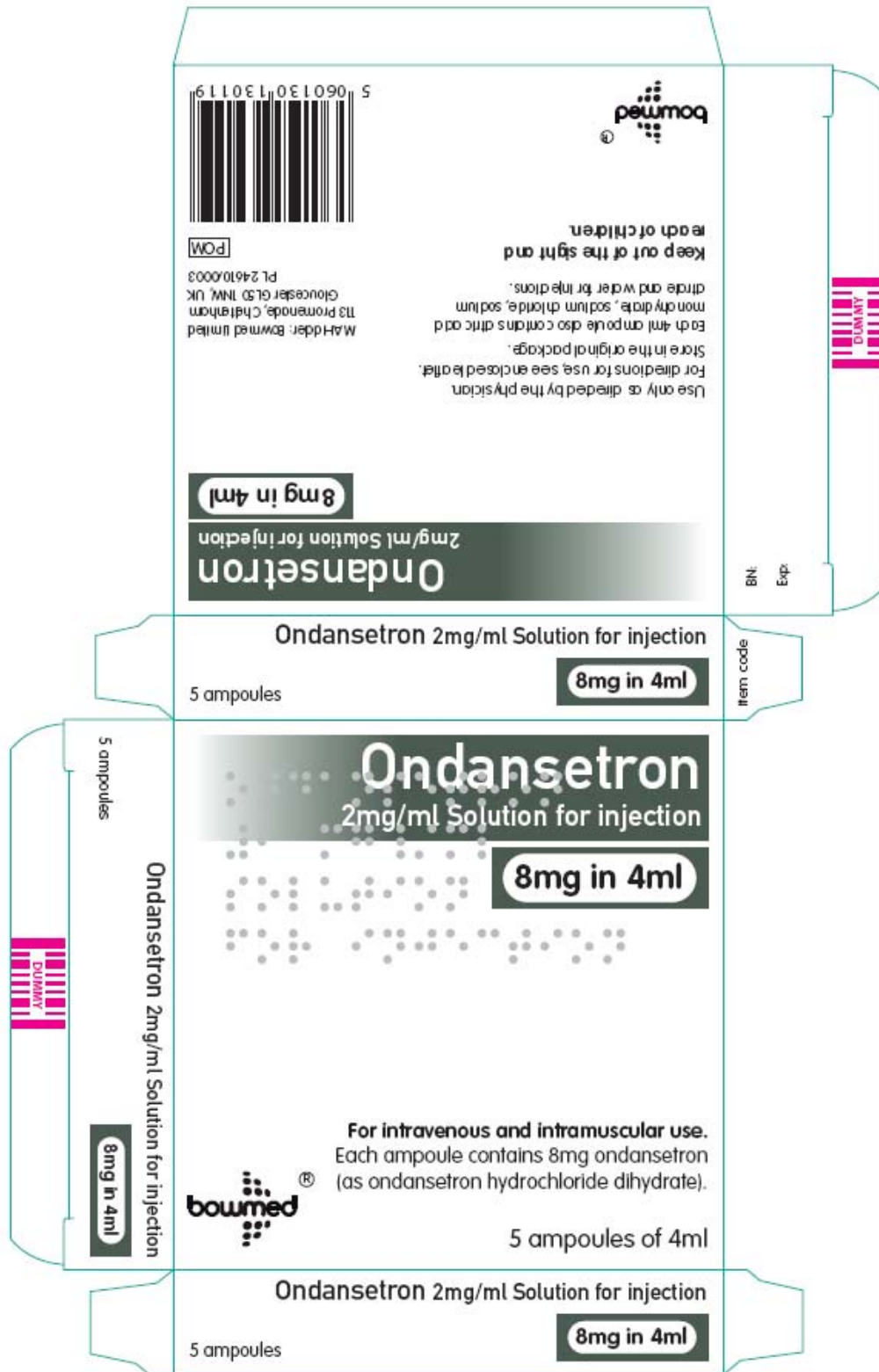
Ondansetron **4mg in 2ml**
2mg/ml Solution for injection
IV/IM use.
MAH: Bowmed Limited. PL: 24610/0003

Label - 4mg in 2ml



Ondansetron
2mg/ml Solution
for injection
4mg in 2ml
IV/IM use.
PL: 24610/0003
BN:
Exp:

Carton – 8mg in 4ml

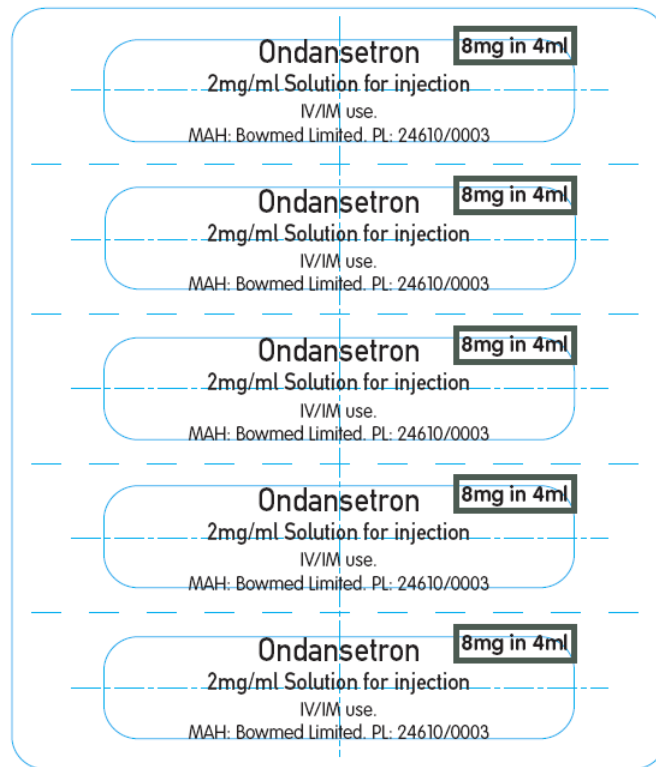


Braille - 8mg in 4ml

Braille text reads as follows (# represents "number sign"):

o n d a n s e t r o n
2 m g / m l
s o l u t i o n
f o r i n j e c t i o n

Foil - 8mg in 4ml



Label - 8mg in 4ml

