Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Ondansetron 2mg/ml Solution for Injection

UK/H/0850/001/MR
UK licence no: PL 04416/0602

Sandoz Ltd

LAY SUMMARY

The MHRA granted Sandoz Ltd a Marketing Authorisation (licence) for the medicinal product Ondansetron 2mg/ml Solution for Injection on 30 July 2007 after a positive conclusion to the Mutual Recognition procedure was agreed on 20 November 2006. This is a prescription only medicine (POM) to be used to stop you from feeling or being sick after surgical operation, chemotherapy or radiotherapy.

Ondansetron hydrochloride dihydrate belongs to a group of drugs known as anti-emetics.

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

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Module 1

Information About Initial Procedure

Product Name	Ondansetron 2mg/ml Solution for Injection
Type of Application	Generic, Article 10.1
Active Substance	Ondansetron hydrochloride dihydrate
Form	Solution for injection
Strength	2mg/ml
MA Holder	Sandoz Ltd 37 Woolmer Way Bordon Hampshire GU35 9QE UK
RMS	United Kingdom
CMS	Austria, Belgium, Czech Republic, Denmark, Estonia, Lithuania, Latvia, Poland, Portugal, Sweeden, Slovenia, Slovakia and Spain.
Procedure Number	UK/H/0850/001/MR
Timetable	Day 60 – 20 November 2006

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains ondansetron hydrochloride dihydrate equivalent to 2 mg ondansetron.

2 ml ampoules contain ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron.

4 ml ampoules contain ondansetron hydrochloride dihydrate equivalent to 8 mg ondansetron.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

Colourless and clear liquid, practically odourless, free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

For intravenous injection or for intravenous infusion after dilution.

For instructions on dilution of the product before administration, see section 6.6.

<u>Chemotherapy and radiotherapy induced nausea and vomiting:</u>

Adults

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

Emetogenic chemotherapy and radiotherapy

Ondansetron can be given either by rectal, oral (tablets or syrup), or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8 mg should be administered as a slow intravenous injection or as a short-time intravenous infusion over 15 minutes immediately before treatment, followed by 8 mg orally twelve hourly.

For oral or rectal administration refer to the SmPC of ondansetron tablets and suppositories, respectively.

Highly emetogenic chemotherapy

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given by intravenous administration. Ondansetron 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 injection immediately before chemotherapy.

- A dose of 8 mg by slow intravenous injection or as a short-time intravenous infusion over 15 minutes immediately before chemotherapy, followed by two further intravenous 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 50-100ml of sodium chloride 9 mg/ml (0.9% w/v) solution saline or other compatible infusion fluid (see compatibility with solutions for infusion under section 6.6) and infused over not less than 15 minutes immediately before chemotherapy.

Doses of greater than 8 mg and up to 32 mg of ondansetron may only be given by intravenous infusion over not less than 15 minutes.

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

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

Children (aged 2 years and above) and adolescents (< 18 years)

Experience in paediatric patients is limited.

In children older than two years ondansetron may be administered as a single intravenous dose of 5 mg/m2 over 15 min immediately before chemotherapy, followed by an oral dose twelve hours later.

There is no experience in children younger than 2 years old.

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

Please refer also to “Special Populations”.

Delayed nausea and vomiting associated with chemotherapy or radiotherapy:

Prescribers intending to use ondansetron in the prevention of delayed nausea and vomiting associated with chemotherapy or radiotherapy in adults, adolescents or children should take into consideration current practice and appropriate guidelines.

Post-operative nausea and vomiting (PONV):

Adults

For the prevention of PONV ondansetron can be administered orally or by intravenous injection. Ondansetron may be administered as a single dose of 4 mg given by slow intravenous injection at induction of anaesthesia. For oral administration refer to the SmPC of ondansetron tablets.

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

Children (aged 2 years and over) and adolescents (< 18 years)

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 0.1 mg/kg up to a maximum of 4 mg 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 0.1 mg/kg up to a maximum of 4 mg.

There is limited data on the use of ondansetron in the prevention and treatment of PONV in children under 2 years of age.

Elderly

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

Please refer also to “Special Populations”.

Special Populations

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 ondansetron or to other selective 5-HT3-receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients.

4.4 Special warnings and precautions for use

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

The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.

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

As there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is coadministered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

The benefit/risk balance of ondansetron prescription should be evaluated in patients having a previous alteration of the QT interval (see section 4.8).

In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

The medicinal product contains 2.4 mmol sodium per maximum dose (32 mg). To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of ondansetron on other medicinal products

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, alfentanil, propofol, and thiopental.

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

Effects of other medicinal products on ondansetron

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.

4.6 Pregnancy and lactation

Pregnancy:

Data on a limited number of exposed pregnancies indicate no adverse effects of ondansetron on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). However animal studies are not always predictive of human response. Caution should be exercised when prescribing to pregnant women, especially in the first trimenon. A careful risk/benefit assessment should be performed.

Lactation:

Tests have shown that ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

In this section undesirable effects are defined as follows: Very common (> 1/10); common

(> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000);

very rare (<1/10,000), including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders

Rare: Immediate hypersensitivity reactions, sometimes severe including anaphylaxis. Anaphylaxis may be fatal. Hypersensitivity reactions were also observed in patients, who were sensitive towards other selective 5-HT3-antagonists.

Nervous system disorders

Rare: There have been reports suggestive of involuntary movement disorders such as extrapyramidal reactions, e.g. oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects.

Cardiac disorders

Rare: Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia. Chest pain and cardiac arrhythmias may be fatal in individual cases.

Very rare: Transitory changes in the electrocardiogram, including prolongation of the QT interval have been observed predominantly after intravenous application of ondansetron.

Gastrointestinal disorders

Common: Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepato-biliary disorders

Uncommon: Asymptomatic increases in liver function tests were observed. These reactions were frequently observed in patients under chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

Common: Headache, sensations of flushing or warmth, hiccups.

Rare: Transient visual disturbances (e.g. blurred vision) and dizziness during rapid intravenous administration of ondansetron.

In individual cases transitory blindness was reported in patients receiving chemotherapeutic agents included cisplatin. Most of reported cases were resolved in 20 minutes.

4.9 Overdose

Symptoms

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.

Treatment

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 (5HT3) antagonists

ATC code: A04AA01

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.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (Bioavailability is about 60 %.). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg 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.

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

Distribution

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

Ondansetron is not highly protein bound (70-76%).

Metabolism

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Excretion

Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half life is about 3 hours.

Special groups

Children

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 2 mg (3-7 years old) or 4 mg (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 100 ml/min at 3 years. Volume of distribution fell from about 75 l at 12 years to 17 l at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

Elderly persons

Studies in healthy elderly volunteers have shown slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).

Renal impairment

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 (5.4 h). 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.

Hepatic impairment

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

Gender differences

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).

5.3 Preclinical safety data

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

Ondansetron and its metabolites accumulate in the milk of rats; milk/plasma-ratio was 5.2.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

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

3 years (unopened);

After opening (and dilution) : Store at 2-8°C and use within 24 hours

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

6.4 Special precautions for storage

Keep the ampoules in the outer carton.

Protect from light.

Under normal room lighting conditions or daylight for at least 24 hours, no protection from light is necessary while infusion takes place.

For storage conditions of the unopened and the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I amber glass ampoules.

2ml ampoules and 4 ml ampoules

Pack sizes: 1, 2, 5, 6, 10 and 5 x 5 ampoules packed in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Compatibility with intravenous fluids.

Ondansetron 2 mg/ml solution for injection should only be admixed with those infusion solutions which are recommended:

Sodium Chloride Intravenous Infusion 9 mg/ml (0.9%w/v)

Glucose Intravenous Infusion 50 mg/ml (5%w/v)

Mannitol Intravenous Infusion 100mg/ml (10%w/v)

Ringers Intravenous Infusion

Potassium Chloride 3mg/ml (0.3%w/v) and Sodium Chloride 9mg/ml (0.9%w/v) Intravenous Infusion

Potassium Chloride 3mg/ml (0.3%w/v) and Glucose 50mg/ml (5%w/v) Intravenous Infusion

Either in type I glass bottles or plastic infusion bags.

Compatibility with other drugs: Ondansetron 2 mg/ml solution for 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 2 mg/ml solution for injection 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 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 1 g, reconstituted with water for injections, 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, 5 ml per 10 mg 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 -2.5mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for ondansetron.

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd.

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0602

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st July 2005

10 DATE OF REVISION OF THE TEXT

07/08/2007

Module 3
Patient Information Leaflet

SANDOZ PACKAGE LEAFLET: INFORMATION FOR THE USER item code

Ondansetron 2 mg/ml Solution for Injection
Ondansetron

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 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 listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

Ondansetron belongs to a group of medicines called anti-emetics, drugs against feeling sick (nausea) or being sick (vomiting).
This medicine is used to stop you from feeling or being sick after surgical operation, chemotherapy, or radiotherapy.

2. Before you use Ondansetron Solution for Injection

Ondansetron Solution for Injection is not suitable for everyone.

Do not use this medicine if you are allergic (hypersensitive) to:
- ondansetron.
- similar medicines to ondansetron such as granisetron or dolasetron.
- any of the other ingredients of this medicine (see section 6).

Ask your doctor or pharmacist if you are not sure about anything before you are given Ondansetron Solution for Injection.

Take special care with Ondansetron Solution for Injection and tell your doctor:
- if you suffer from any blockage in your gut or if you have severe constipation.
- if you have cardiac problems.
- if you have liver problems.
- if you are having your tonsils out.

This medicine should not be used in children under 2 years of age, because insufficient experience is available.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you are taking phenytoin, carbamazepin (used to treat epilepsy or other illnesses), or rifampicin (used to treat certain infections): the ondansetron blood concentrations are decreased.
If you are taking tramadol (used to treat pain): the effect of tramadol may be reduced.

Pregnancy and breast-feeding:
- Because of insufficient experience the use of ondansetron during pregnancy is not recommended.
- Ondansetron enters the breast milk, so you should not breast feed while you are having this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ondansetron has no or negligible effect on the ability to drive or use machines.

Important information about some of the ingredients of Ondansetron Solution for Injection
This medicinal product contains 2.3 mmol (53.5 mg) sodium per maximum daily dose. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Ondansetron Solution for Injection

This medicine is administered as intravenous injection (into a vein) or, after dilution, as intravenous infusion (for a longer time). It will usually be given by a doctor or a nurse.

Dosage
Your doctor will decide on the correct dose of ondansetron therapy for you.
The dose varies depending on your medicinal treatment (chemotherapy or surgery), on your liver function and on whether it is given by injection or infusion.
In case of chemotherapy or radiotherapy the usual dose in adults is 8 – 32 mg ondansetron a day. For treatment of post-operative nausea and vomiting usually a single dose of 4-8 mg ondansetron is administered.

Children older than two years and adolescents
In case of chemotherapy or radiotherapy the usual dose in children and adolescents is 5 mg per square meter of their body surface area.
For treatment of post-operative nausea and vomiting 0.1 mg ondansetron per kg body weight up to a maximum dose of 4 mg is administered into a vein.

This medicine should not be used in children younger than two years.

Dosage adjustment

Patients with hepatic impairment:
In patients having hepatic problems the dose has to be adjusted to a maximum daily dose of 8 mg ondansetron.

Elderly as well as patients with renal impairment or poor sparteine/debrisoquine metabolism:
No alteration of daily dosage or frequency of dosing or route of administration is required.

Duration of treatment
Your doctor will decide on the duration of ondansetron therapy for you.

item code

If you receive more of this medicine than you should
Little is known at present about overdosage with ondansetron. In a few patients, the following effects were observed after overdose: visual disturbances, severe constipation, low blood pressure and unconsciousness. In all cases, the symptoms disappeared completely.
There is no specific antidote to ondansetron; for that reason, if overdose is suspected, only the symptoms should be treated.
Tell your doctor if any of these symptoms occur.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

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

Serious side effects:
• Tell your doctor or nurse straight away if you experience any of the following:
Serious allergic reaction which causes swelling of the face or throat, difficulty in breathing or dizziness, or severe itching of the skin with raised lumps.
• Chest pain or irregular heart beat.

Other side effects
Tell your doctor if any of the following side effects bother you:

Common side effects (affects less than 1 in 10 people) include: headache, constipation, hiccups, feeling flushed or warm.

Uncommon side effects (affects less than 1 in 100 people) include: increases in liver blood test results, local irritation around the injection side (e.g. skin rash or swelling, itching), sometimes extending along the drug administration vein.

Rare side effects (affects less than 1 in 1000 people) include: fits (seizures), problems with eye movements or spasms in the muscles or the head and neck, blurred vision, transient blindness, dizziness, low blood pressure, slow heart beat.

Very rare side effects (affects less than 1 in 10,000 people) include: electrocardiogram alterations.

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 pharmacist.

5. How to store Ondansetron Solution for Injection

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label after EXP (abbreviation used for expiry date). The expiry date refers to the last day of that month.

Keep the ampoules in the outer carton, in order to protect from light.

Dilutions of Ondansetron Solution for Injection in compatible intravenous infusion liquids should be stored at 2-8°C and discarded after 24 hours. The diluted infusion is stable under normal room lighting conditions or daylight for at least 24 hours. Therefore, no protection from light is necessary while infusion takes place.

Do not use Ondansetron Solution for Injection if you notice signs of deterioration such as colouration of the solution or when particles are visible.

Do not throw away any medicines through wastewater or household waste. Ask your pharmacist how to get rid of medicines that you no longer need. This will help to protect the environment.

6. Further Information

What Ondansetron 2 mg/ml Solution for Injection contains
The active substance is ondansetron.
Each ml solution for injection contains 2 mg ondansetron (as hydrochloride dihydrate).

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

What this medicine looks like and contents of the pack
Ondansetron Solution for Injection is a clear and colourless liquid that is odourless and free of particles. It is available in cartons of 1, 2, 5, 6, 10 or 5 x 5 glass ampoules. Not all pack sizes may be marketed.
The glass ampoules are available as ampoules containing 2 ml respectively 4 ml solution for injection.

Marketing Authorisation Holder and Manufacturer

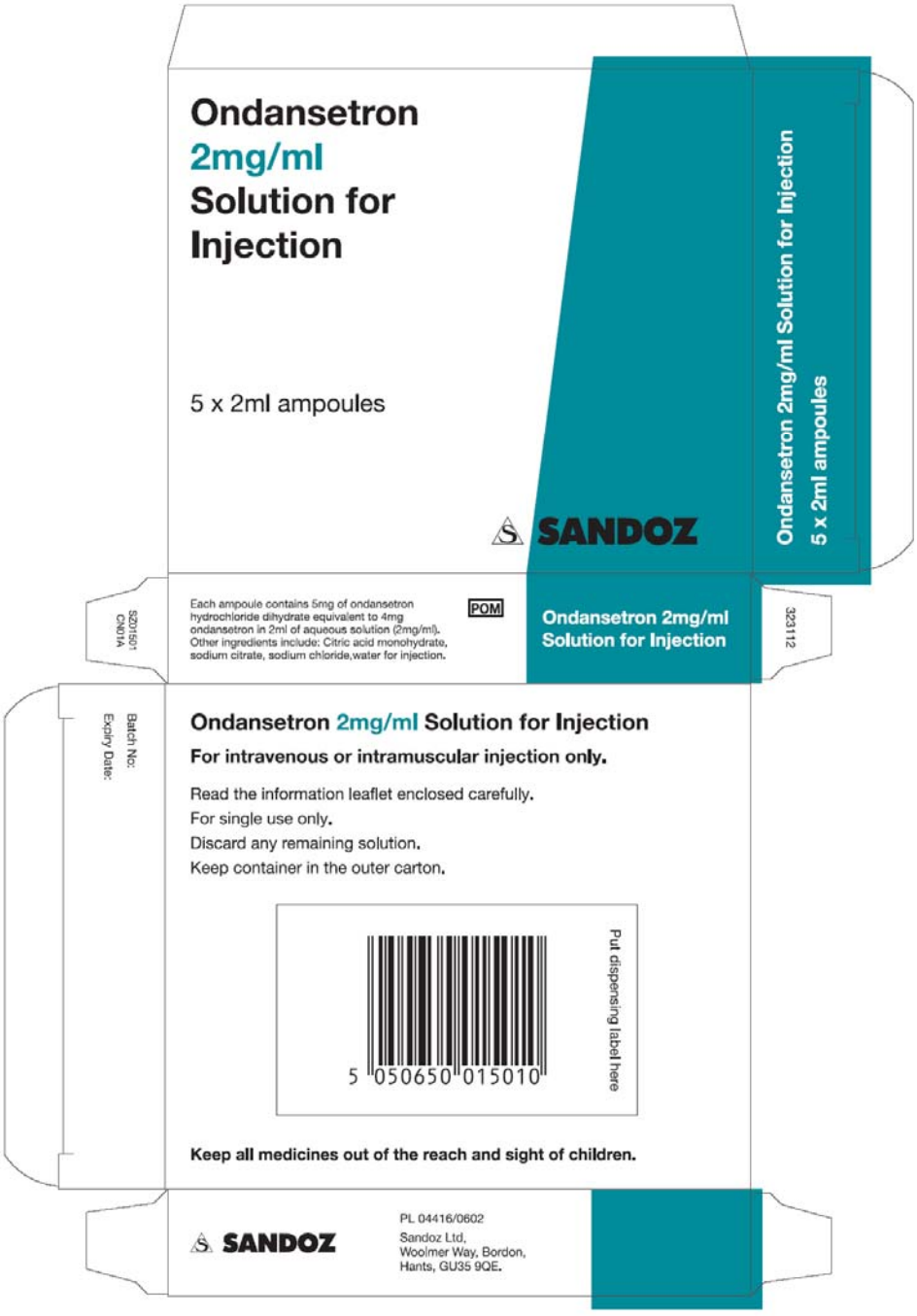
Marketing Authorisation Holder:
Sandoz Ltd, 37 Woolmer Way, Bordon, Hants, GU35 9QE, U.K.

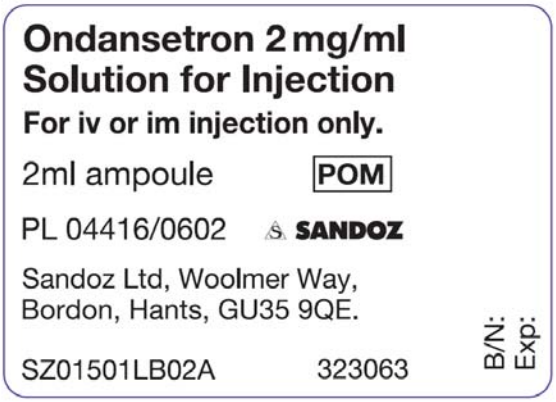
Manufacturer:
Lek Pharmaceuticals d.d, Verovškova 57, 1000 Ljubljana, Slovenia.

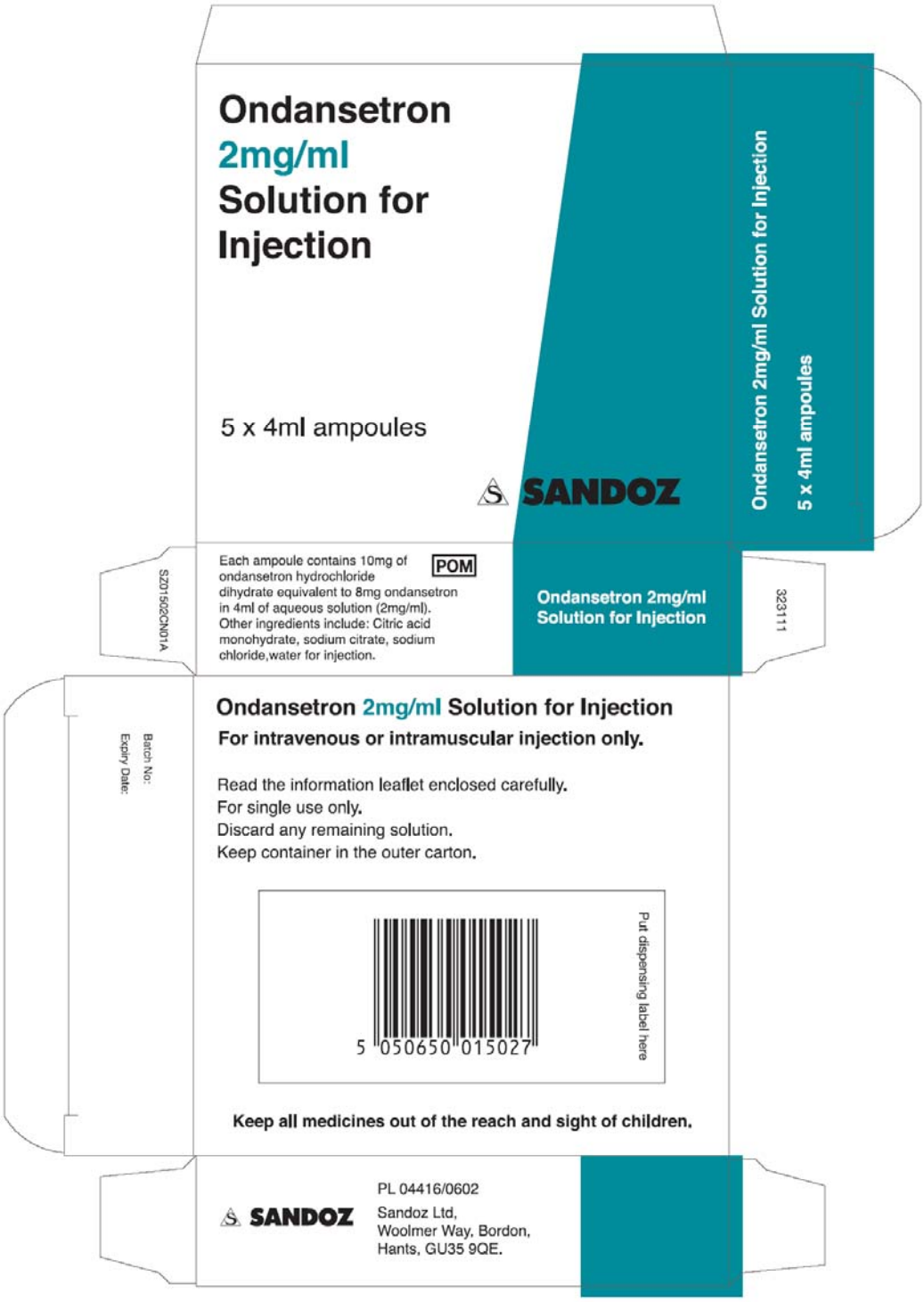
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

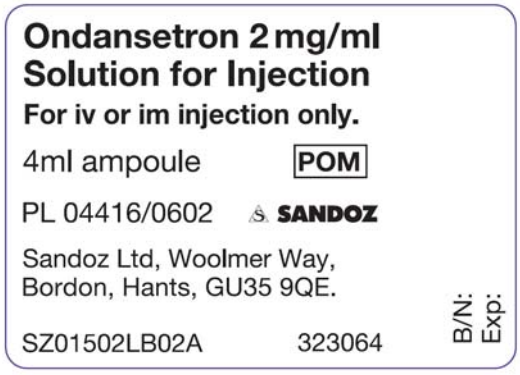
This leaflet was last approved in: 04/2007 (to be amended after approval)

Module 4
Labelling






Ondansetron
2mg/ml
Solution for
Injection
5 x 4ml ampoules
SANDOZ
Ondansetron 2mg/ml Solution for Injection
5 x 4ml ampoules
Each ampoule contains 10mg of ondansetron hydrochloride dihydrate equivalent to 8mg ondansetron in 4ml of aqueous solution (2mg/ml). Other ingredients include: Citric acid monohydrate, sodium citrate, sodium chloride,water for injection.
POM
Ondansetron 2mg/ml Solution for Injection
SZ01502CN01A
323111
Batch No:
Expiry Date:
Ondansetron 2mg/ml Solution for Injection
For intravenous or intramuscular injection only.
Read the information leaflet enclosed carefully.
For single use only.
Discard any remaining solution.
Keep container in the outer carton.
5 050650 015027
Put dispensing label here
Keep all medicines out of the reach and sight of children.
SANDOZ
PL 04416/0602
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.


Ondansetron 2 mg/ml
Solution for Injection
For iv or im injection only.
4ml ampoule
POM
PL 04416/0602
SANDOZ
Sandoz Ltd, Woolmer Way,
Bordon, Hants, GU35 9QE.
SZ01502LB02A
323064
B/N:
Exp:

Module 5

Scientific Discussion During Initial Procedure

I 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 Solution for Injection (PL 04416/0602) on 30 July 2007. The product is a prescription only medicine.

This application is made under Article 10.1 of 2001/83 EC, as amended, claiming that Ondansetron 2mg/ml Solution for Injection is a generic product of Zofran Injection 2mg/ml (Glaxo Operations UK Ltd, trading as GlaxoSmithKline UK) which was granted a licence in March 1990.

The product contains the active ingredient ondansetron and is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV).

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

No new preclinical studies were conducted, which is acceptable given that the application was based on a reference product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on a reference product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The Mutual Recognition procedure was completed at Day 60 (20 November 2006), with the RMS and the CMSs agreeing that the licence was approvable. The national phase of the Mutual Recognition procedure was completed in the UK on 30 July 2007.

II ABOUT THE PRODUCT

Name of the product in the Reference Member State	Ondansetron 2mg/ml Solution for Injection
Name(s) of the active substance(s) (INN)	Ondansetron hydrochloride dihydrate
Pharmacotherapeutic classification (ATC code)	Serotonin (5HT3) antagonists (A04AA01)
Pharmaceutical form and strength(s)	Solution for injection 2mg/ml
Reference numbers for the Mutual Recognition Procedure	UK/H/0850/001/MR
Reference Member State	United Kingdom
Concerned Member States	Austria, Belgium, Czech Republic, Denmark, Estonia, Lithuania, Latvia, Poland, Portugal, Sweeden, Slovenia, Slovakia and Spain.
Marketing Authorisation Number(s)	PL 04416/0602
Name and address of the authorisation holder	Sandoz Ltd 37 Woolmer Way Bordon Hampshire GU35 9QE UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Ondansetron hydrochloride dihydrate
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 specification based on the European Pharmacopoeia monograph is provided for ondansetron hydrochloride dihydrate.

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

Batch analysis data are provided for five commercial scale batches and comply with the proposed specification.

Ondansetron hydrochloride dihydrate is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 3 years when stored in the proposed packaging protected from light.

DRUG PRODUCT

Other Ingredients
The excipients present are citric acid monohydrate, sodium citrate, sodium chloride and waster for injections.

The excipients used comply with their respective European Pharmacopoiea monographs. Satisfactory certificates of analysis have been provided.

No excipients used contain material of animal or human origin.

Pharmaceutical Development
The applicant has provided suitable product development rationale and data.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and the results are satisfactory.

Control of Drug Product
The proposed finished product specification is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specifications.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
The finished product is packaged in 2ml and 4ml Type I amber glass ampoules in pack sizes of 1, 2, 5, 6, 10, and 25 ampoules. Satisfactory specifications and certificates of analysis have been provided for the packaging components.

Stability of the Drug Product
The stability data provided support a shelf-life of 3 years, with storage conditions "Keep the ampoules in the outer carton. Protect from light". After opening (and dilution) the solution should be stored at 2-8°C and used within 24 hours.

Bioequivalence/Bioavailability
Not required for an application of this type.

SPC, PIL, Labels
The SPC and labels are pharmaceutically acceptable.

The Patient Information Leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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 on the information that it contains.

III.2 PRE-CLINICAL ASPECTS

No new non-clinical data have been supplied with this application and none are required for an application of this type. The non-clinical overview gives an adequate update on the known pharmacological and toxicological properties of ondansetron.

III.3 CLINICAL ASPECTS

Clinical Pharmacology
No original data on the formulation proposed for marketing have been submitted for assessment. A Clinical Overview has been submitted which 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.

Clinical efficacy
No new efficacy data have been submitted for this application and none are required.

Clinical safety
No new safety data have been submitted for this application and none are required.

Expert Report
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical doctor.

Summary of Product Characteristics (SPC)
This is satisfactory and consistent with the SPC for the reference product.

Patient Information Leaflet (PIL)
This is satisfactory and consistent with the SPC.

Labelling
These are satisfactory.

Conclusion
There are no clinical objections to the grant of a Marketing Authorisation for this application.

IV OVERALL CONCLUSION AND BENEFIT/RISK 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

No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT

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

Module 6

Steps Taken After Initial Procedure - Summary

Date submitted	Application type	Scope	Outcome
31 Dec 2007	Type IB MR Variation	To change the name of the product in Austria from Ondansetron Hexal 2mg/ml-Ampullen to Ondansetron Hexal 2mg/ml-Injektionsloesung	Approved 25 Feb 2008