

Public Assessment Report
Decentralised Procedure

Ondansetron 2mg/ml Solution for Injection

UK/H/1250/001/DC

UK licence no: PL 20075/0082

Accord Healthcare Limited

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Noridem Enterprises Limited a Marketing Authorisation (licence) for the medicinal product Ondansetron 2mg/ml Solution for Injection (PL 20075/0082). This prescription-only medicine (POM) is used in the management of nausea or vomiting as a result of cancer chemotherapy/radiotherapy, and for the prevention of post-operative nausea and vomiting in adults and children.

Ondansetron Injection contains the active ingredient ondansetron which is an antiemetic medicine.

The test product was considered equivalent to the reference product Zofran Injection 2mg/ml (GlaxoSmith Kline), first registered on 8th January 1991 (The Netherlands).

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

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Module 1

Product Name	Ondansetron 2mg/ml Solution for Injection or Infusion
Type of Application	Generic, Article 10.1
Active Substance	Ondansetron (as hydrochloride dihydrate)
Form	Solution For Injection or Infusion
Strength	2mg/ml
MA Holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, Harrow, Middlesex HA1 4HF UK
RMS	UK
CMS	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Finland, Hungary, Ireland, Italy, Latvia, Malta, Norway, Poland, Portugal, Sweden, Slovenia, Slovak Republic and Spain.
Procedure Number	UK/H/1250/001/DC
Timetable	Day 210 – 5 th November 2009

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 2 mg ondansetron (as ondansetron hydrochloride dihydrate)

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

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

1 ml solution for injection or infusion contains 3.62 mg of sodium as sodium citrate, sodium chloride and sodium hydroxide.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

Clear colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, Prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:

Management of chemotherapy-induced nausea and vomiting in children aged ≥ 6 months.

Prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month.

4.2 Posology and method of administration

For intravenous injection or intramuscular injection or intravenous infusion after dilution.

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

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.

Chemotherapy and radiotherapy induced nausea and vomiting:

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

Emetogenic chemotherapy and radiotherapy:

For patient receiving Emetogenic chemotherapy and radiotherapy, ondansetron can be given either by intravenous or intramuscular or other routes of administration. However this product is for injection or infusion only.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron associated with dexametasone should be continued for up to 5 days after a course of treatment. Ondansetron treatment with other dosage forms than intravenous 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 can be given either by intravenous or intramuscular 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 or intramuscular injection immediately before chemotherapy.
- A dose of 8 mg by slow intravenous or intramuscular injection or as a short-time intravenous infusion over 15 minutes immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.
- Doses of greater than 8mg and up to 32 mg of ondansetron may only be given by intravenous infusion diluted in 50-100 ml of saline (0.9% w/v) or other compatible infusion fluid (*see section 6.6*) and 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.

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.

Paediatric Population:

Chemotherapy-induced nausea and vomiting in children aged ≥ 6 months and adolescents:

The dose of chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing – see sections 4.4 and 5.1

There are no data from controlled clinical trials on the use of Ondansetron Injection in the prevention of chemotherapy-induced delayed or prolonged nausea and vomiting. There are no data from controlled clinical trials on the use of Ondansetron Injection for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m². The intravenous dose must not exceed 8 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.

The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥ 6 months and adolescents

BSA	Day 1 ^{a,b}	Days 2-6 ^b
< 0.6 m ²	5 mg/m ² i.v. 2 mg syrup or tablet after 12 hours	2 mg syrup or tablet every 12 hours
> 0.6 m ²	5 mg/m ² i.v. 4 mg syrup or	4 mg syrup or tablet every 12

	tablet after 12 hours	hours
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^a The intravenous dose must not exceed 8 mg.

^b The total daily dose must not exceed adult dose of 32 mg.

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing – see sections 4.4 and 5.1. Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/Kg. The intravenous dose must not exceed 8 mg.

Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 2 below.

Table 2: Weight-based dosing for Chemotherapy - Children aged ≥ 6 months and adolescents

Weight	Day1 ^{a,b}	Days 2-6 ^b
≤ 10 kg	Up to 3 doses of 0.15 mg/kg at 4-hourly intervals.	2 mg syrup or tablet every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg at 4-hourly intervals.	4 mg syrup or tablet every 12 hours

^a The intravenous dose must not exceed 8 mg.

^b The total daily dose must not exceed adult dose of 32 mg.

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

Please refer also to ‘Special Populations.’

Post-operative nausea and vomiting (PONV):

Prevention of PONV

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

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

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

Paediatric population:

Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents.

Oral Formulation: No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post operative nausea and vomiting; slow i.v. injection is recommended for this purpose.

Injection: For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose 0.1 mg/Kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

There are no data on the use of Ondansetron Injection for the treatment of postoperative vomiting 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 is required.

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

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

4.3 **Contraindications**

Hypersensitivity to ondansetron or to other selective 5HT₃ receptor antagonists (e.g. granisetron, dolasetron) 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.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitive reactions.

Paediatric Population:

Paediatric population receiving ondansetron with hepatotoxic chemotherapeutical agents should be monitored closely for impaired hepatic function.

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. Very rarely and predominantly with intravenous Ondansetron, transient ECG changes including QT interval prolongation have been reported. Caution is advised if patients have received cardiotoxic agents and in patients with a history or family history of prolonged QT syndrome (see section 4.8).

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

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

This medicinal product contains 2.5 mmol (or 57.9 mg) sodium per maximum daily dose of 32 mg. To be taken into consideration by patients on a controlled sodium diet.

Chemotherapy-induced nausea and vomiting:

When calculating the dose on a mg/Kg basis and administering three doses at 4 hourly intervals, the total daily dose will be higher than if one single dose of 5 mg/m² followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross trial comparing indicate similar efficacy for both regimens – see section 5.1

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, temazepan, furosemide, propofol, alfentanil or 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.

Use of Ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of Ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias (See section 4.4).

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 fetus, 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. If it is absolutely necessary that Ondansetron be given caution should be exercised when prescribing to pregnant women especially in the first trimester. A careful risk/benefit assessment should be performed.

Lactation

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

4.7 Effects on ability to drive and use machines

Ondansetron 2mg/ml has no or negligible 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 (>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) not known (cannot be estimated from the available data).

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis. Anaphylaxis may be fatal.

Cross-sensitivity has also been observed in patients who are hypersensitive to other selective 5HT₃ antagonists.

Nervous system disorders

Very common: Headache.

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. Dizziness during rapid i.v. administration.

Eye disorders

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

Very rare: Transient blindness predominantly during intravenous administration.

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

Cardiac disorders

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 administration of ondansetron.

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.

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

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests.

These events were most frequently observed in patients receiving 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.

Paediatric population

The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (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.

Paediatric Population:

Chemotherapy-induced nausea and vomiting

The efficacy of Ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years. On the days of chemotherapy, patients received either ondansetron 5 mg/m² i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/Kg i.v. + after 8-12 hrs placebo p.o. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49 % (5mg/m² i.v. + ondansetron 4 mg p.o.) and 41 % (0.45 mg/Kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. A double-blind randomise placebo-controlled trial in 438 aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in 73% of patients when ondansetron was administered intravenously at a dose of 5mg/m² i.v. together with 2-4 mg dexamethasone p.o. and in 71% of the patients when ondansetron was administered as a syrup at a dose of 8 mg + 2-4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study. All children receive three 0.15 mg/Kg doses of intravenous ondansetron, administered at 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients. Another open-label, non-operative, single-arm study investigated the efficacy of one intravenous dose of 0.15 mg/Kg ondansetron followed by two ondansetron doses of 4mg for children aged < 12 yrs and 8 mg for children aged ≥ 12yrs (total no. of children n = 28). Complete control of emesis was achieved in 42% of patients.

Prevention of post-operative nausea and vomiting

The efficacy of a single dose of Ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 3 Kg). Induced subjects were scheduled to undergo effective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/Kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11% p<0.0001).

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 30ng/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 4mg 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 terminal half life of about 3 hours and 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 Patient Populations

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.

Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age

Study	Patient population (intravenous dose)	Age	N	AUC (ng.h/mL)	CL (L/h/Kg)	V _{S55} (L/Kg)	T _{1/2} (h)
				Geometric Mean			Mean
S3A40319 ¹	Surgery (0.1 or 0.2 mg/kg)	1 to 4 months	19	360	0.401	3.5	6.7
S3A40319 ¹	Surgery (0.1 or 0.2 mg/kg)	5 to 24 months	22	236	0.581	2.3	2.9
S3A40320 & S3A40319 Pop PK ^{2,3}	Cancer/Surgery (0.15 mg/kg q4h/0.1 or 0.2 mg/Kg)	1 to 48 months	115	257	0.582	3.65	4.9
S3KG02 ⁴	Surgery (2 mg or 4 mg)	3 to 12 years	21	240	0.439	1.65	2.9
S3A-150	Cancer (0.15 mg/kg q4h)	4 to 18 years	21	247	0.599	1.9	2.8

¹ Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg

² Population PK Patients: 64% cancer patients and 36% surgery patients.

³ Population estimates shown; AUC based on dose of 0.15 mg/kg.

⁴ Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

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

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. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

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 and carcinogenic potential.

Ondansetron and its metabolites accumulate in the milk of rats at a milk: plasma ratio of 5.2:1.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)
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

Unopened

2 years

Injection

After first opening the medicinal product should be used immediately.

Infusion

Chemical and physical in-use stability has been demonstrated for 7 days at 25°C and 2-8°C with the solutions given in section 6.6.

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

6.4 Special precautions for storage

Store below 25°C. Keep ampoules in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Type I clear glass ampoules

2 ml:

Pack sizes: Carton containing 10 ampoules.
 Carton containing 5 ampoules.

4 ml:

Pack sizes: Carton containing 10 ampoules.
 Carton containing 5 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution must not be sterilized in an autoclave.

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

The stability of Ondansetron Injection after dilution with the recommended infusion fluids have been demonstrated in concentrations 0.016 mg/ml and 0.64 mg/ml.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags with polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes. Dilutions of Ondansetron Injection in 10% mannitol injection, ringer's injection, 0.3% potassium chloride and 0.9% sodium chloride injection, 0.3% potassium chloride and 5% dextrose injection, 0.9% sodium chloride injection and 5% glucose injection have been demonstrated to be stable in polyvinyl chloride infusion bags and polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes.

Compatibility with other drugs: Ondansetron Injection may be administered by intravenous infusion using 0.9% sodium chloride and 5% dextrose injection 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 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.

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

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

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

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

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

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 50-100 ml 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 - 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 0.75 mg/ml for ondansetron.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

The diluted solutions should be stored protected from light.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/12/2009

10 DATE OF REVISION OF THE TEXT

11/12/2009

Module 3

Product Information Leaflet



PACKAGE LEAFLET: INFORMATION FOR THE USER

Ondansetron 2 mg/ml Solution for Injection or Infusion

Ondansetron

Read this entire leaflet carefully before you start using this medicine
 • Keep this leaflet. You may need to read it again.
 • If you have further questions, please ask your doctor or your pharmacist.
 • This medicine has been prescribed for you. 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.

The name of the medicinal product is Ondansetron 2mg/ml Solution for Injection or infusion but will be referred to as Ondansetron injection throughout the package leaflet.

In this leaflet:

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

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

Ondansetron injection contains the active ingredient ondansetron, which belongs to a group of medicines called anti-emetics.

Ondansetron injection is used for

- Preventing nausea (feel sick) and vomiting (be sick) caused by chemotherapy or radiotherapy for cancer in adults and in children aged ≥ 6 months.
- Preventing nausea and vomiting after surgery in adults and in children aged ≥ 1 month.

Ask your doctor, nurse or pharmacist if you would like any further explanation about this uses.

The following information is intended for medical or healthcare professionals only

Instructions for use:

For intravenous injection or intramuscular injection or intravenous infusion after dilution.
 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.
 Chemotherapy and radiotherapy induced nausea and vomiting:
 Adults: The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of ondansetron should be flexible in the range of 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy:
 For patient receiving Emetogenic chemotherapy and radiotherapy, ondansetron can be given either by intravenous or intramuscular or other routes of administration. However this product is for injection or infusion only.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron associated with dexamethasone should be continued for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy: For patients receiving highly

2. Before Ondansetron injection is given to you

Ondansetron injection must not be given to you (please tell your doctor) if you are allergic (hypersensitive) to Ondansetron or any of the other ingredients of Ondansetron injection or to any similar medicines e.g. granisetron or dolasetron.

Take Special care with Ondansetron injection

- If you have a blockage in your gut or suffer from severe constipation Ondansetron can make these conditions worse.
 - If you have been told your liver is not working as well as it should
 - If you have a problem with your heart or are taking medicines used to treat heart problems
 - If you are having surgery to remove your tonsils, because treatment with ondansetron may hide symptoms of internal bleeding
 - If your child is being treated & he / she is less than 2 years old, with liver damage.
- Always inform the laboratory during tests of blood and urine that you are being treated with ondansetron.
 If any of the above statements are applicable to you, please tell your doctor before having the injection.

Taking other medicines

Please tell your doctor if you are taking any of the following medicines or have recently taken any other medicines including medicines obtained without a prescription, natural supplements or vitamins or minerals.

You must tell your doctor that you are using Ondansetron, if he/she starts treating you with the following medicine:

- Phenytoin (used to treat epilepsy & heart arrhythmias)
- Carbamazepine (used to treat epilepsy & neuralgic pain)
- Rifampicin (an antibiotic)
- Tramadol (used to treat pain following surgery)

The effect of ondansetron may be weakened if you are taking phenytoin, carbamazepine or rifampicin. The painkilling effect of Tramadol may be weakened if you are taking ondansetron.

Contact your doctor. It may be necessary to adjust the dose.

Using ondansetron injection with food and drink

You may use ondansetron injection independently of food and drink

Pregnancy and breast-feeding:

Pregnancy:
 Because of insufficient experience the use of ondansetron injection in pregnancy is not recommended. If you are pregnant, especially during the

first third of your pregnancy, you should use ondansetron only, if your treating physician has performed a careful benefit/risk assessment.

Breast-Feeding:

The ondansetron in Ondansetron injection may pass into mothers' milk. Therefore mothers receiving ondansetron injection should not breast-feed their baby.
 Ask your doctor for advice before taking any medicine.

Driving and using machines:

Ondansetron injection will not affect your ability to drive or operate machinery.

Important information about some of the ingredients in this medicine
 This medicinal product contains 2.5 mmol (or 57.5 mg) sodium per maximum daily dose of 32 mg. To be taken into consideration by patients on a controlled sodium diet.

3. How Ondansetron injection will be given

Ondansetron injection is normally given by a nurse or doctor. The dose you have been prescribed will depend on the treatment you are having.

To prevent nausea and vomiting from chemotherapy or radiotherapy
 On the day of chemotherapy or radiotherapy the usual adult dose is 8 mg given by an injection into your vein or muscle, just before your treatment, and another 8 mg twelve hours later.

On the following days

- The usual adult intravenous dose does not exceed 8 mg.
 - Oral dosing can commence twelve hours later and may be continued for up to 5 days.
- If your chemotherapy or radiotherapy is likely to cause severe nausea and vomiting, you may be given more than the usual dose of Ondansetron injection. Your doctor will decide this.

Children aged over 6 months and adolescents

The doctor will decide the dose.

On the day of chemotherapy or radiotherapy

- The first dose is given by an injection into the vein, just before your child's treatment. After chemotherapy, your child's medicine will usually be given by mouth; the usual dose is a 4 mg.

To prevent nausea and vomiting after an operation

- The usual dose for adults is 4 mg given by an injection into your vein or muscle. This will be given just before your operation.
- For children aged over 1 month and adolescents, the doctor will decide

use of Ondansetron injection for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m². The intravenous dose must not exceed 8 mg.
 Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.
 The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥6 months and adolescents

BSA	Day 1 ^a	Days 2-6 ^b
< 0.6 m ²	5 mg/m ² i.v. 2 mg syrup or tablet after 12 hours	2 mg syrup or tablet every 12 hours
> 0.6 m ²	5 mg/m ² i.v. 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours

- ^a The intravenous dose must not exceed 8 mg.
- ^b The total daily dose must not exceed adult dose of 32 mg.

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing. Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/Kg. The intravenous dose must not exceed 8 mg.

Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.
 Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 2 below.





the dose. The maximum dose is 4 mg given as an injection into the vein. This will be given just before the operation.

To treat nausea and vomiting after an operation

- The usual adult dose is 4 mg given by an injection into your vein or muscle.
 - For children aged over 1 month and adolescents, the doctor will decide the dose. A single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia. Patients with moderate or severe liver problems
- The total daily dose should not be more than 8 mg.

If you received more Ondansetron Injection than you should

Little is known at present about over dosage with ondansetron. In a few patients, the following effects were seen after overdosage: disturbances of vision, severe constipation, lowered blood pressure and loss of consciousness. In all cases the symptoms disappeared completely. There is no particular antidote to ondansetron. For that reason, if overdose is suspected, only the symptoms should be treated. Tell your doctor or nurse 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, Ondansetron Injection can cause side effects, although not everybody gets them.

SERIOUS SIDE-EFFECTS

Allergic Reactions

These are rare, but allergic (hypersensitivity) reactions can produce a rash and itching as well as more serious symptoms such as swelling of the hands, feet, ankles, face, lips, mouth and/or throat. This can lead to difficulty swallowing and breathing.

Heart rhythm disorders

These are uncommon but can produce palpitations (an unpleasant sensation of an irregular and/or forceful beating of the heart) or a very slow heart beat. There may also be chest pain.

These serious side-effects can be life-threatening, therefore TELL YOUR DOCTOR OR NURSE IMMEDIATELY IF YOU EXPERIENCE ANY OF THE SYMPTOMS ABOVE.

Less serious side-effects:

- Very common
- More than 1 in 10 patients
- Headache

Weight	Day ¹ / ¹⁴	Days 2-6 ^a
≤10 kg	Up to 3 doses of 0.15 mg/kg at 4-hourly intervals.	2 mg syrup or tablet every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg at 4-hourly intervals.	4 mg syrup or tablet every 12 hours

^a The intravenous dose must not exceed 8 mg.
^b The total daily dose must not exceed adult dose of 32 mg.

Elderly: Ondansetron is well tolerated by patients over 65 years and no alteration of dosage; dosing frequency or route of administration is required. Please refer also to 'Special Populations.'

Post-operative nausea and vomiting (PONV):

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

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

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

Paediatric population:

Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents.

Oral Formulation: No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post operative nausea and vomiting; slow i.v. injection is recommended for this purpose

Injection: For prevention of PONV in paediatric patients having surgery

Common

More than 1 in 100, but less than 1 in 10, patients

- Sensations of flushing or warmth
- Constipation
- Hiccups

Uncommon

More than 1 in 1,000, but less than 1 in 100 patients

- Hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.
- Changes in liver function tests (mostly in patients receiving cisplatin chemotherapy)

Rare

More than 1 in 10,000 patients, but less than 1 in 1,000 patients

- Seizures (fits or convulsions)
- Involuntary movements such as upward spasm of the eyes, twisting or jerking movements of the body
- Dizziness while the medicine is being given
- Visual disturbances (e.g. blurred vision)

Very rare

Less than 1 in 10,000 patients, including isolated reports

- Transitory changes in the electrocardiogram
- Temporary loss of vision, usually lasting less than 20 minutes, mostly in patients receiving cisplatin chemotherapy.

If you are going to have any blood tests or liver function test, this medicine may affect the results, so inform your doctor. If you feel unwell or have any unusual discomfort you do not understand, tell your doctor as soon as possible.

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

5. How to store Ondansetron Injection

Keep out of the reach and sight of children.

Do not use Ondansetron Injection after the expiry date, which is stated on the ampoule or carton after EXP. The expiry date refers to last date of that month.

Store below 25°C. Keep ampoules in the outer carton in order to protect from light.

Do not use Ondansetron Injection if you notice container is damaged or particles / crystals are visible.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

There are no data on the use of Ondansetron Injection for the treatment of postoperative vomiting 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 is 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 is required.

Incompatibilities:

The solution must not be sterilised in an autoclave.

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

6. Further information

What Ondansetron Injection contains:

The active ingredient in Ondansetron Injection is ondansetron (as hydrochloride dihydrate).

Each ml of solution for injection or infusion contains 2 mg ondansetron (as ondansetron hydrochloride dihydrate).

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

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

The other ingredients are citric acid monohydrate, sodium citrate, sodium chloride, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injections

What Ondansetron solution for injection or infusion looks like and contents of the pack:

Ondansetron Injection is a clear colourless solution for injection or infusion filled in clear glass ampoules.

Ondansetron Injection 2 mg/ml is available in pack containing 5 X 2 ml and 5 X 4 ml ampoules and also available in 10 X 2 ml and 10 X 4 ml ampoules. Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer:

Accord Healthcare Limited,
 Sage House, 319 Pinner Road,
 North Harrow, Middlesex, HA1 4HF, United Kingdom

The leaflet was last approved in 11/2009.

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

The stability of Ondansetron Injection after dilution with the recommended infusion fluids have been demonstrated in concentrations 0.016 mg/ml and 0.64 mg/ml.

Use only clear and colourless solutions.

The diluted solutions should be stored protected from light.

Shelf-life and storage

Unopened

2 years

Store below 25°C. Keep ampoules in the outer carton in order to protect from light.

Injection

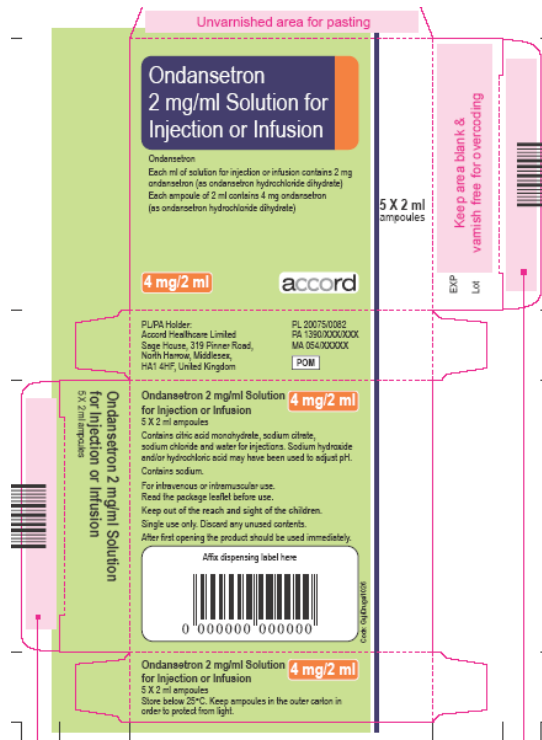
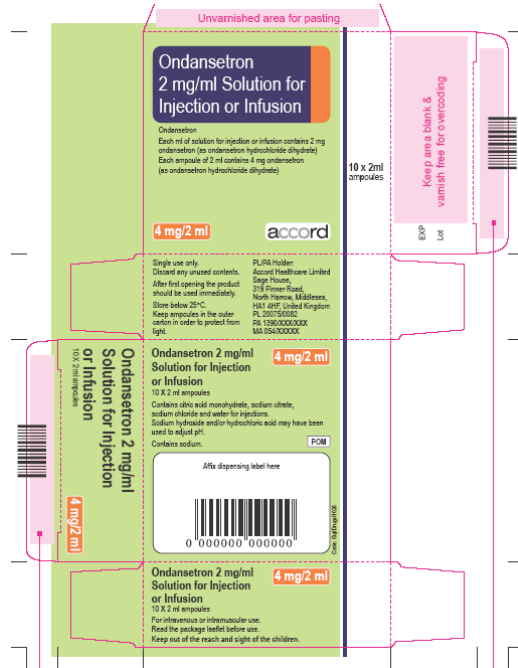
After first opening the medicinal product should be used immediately.

After dilution with recommended diluents chemical and physical in-use stability has been demonstrated for 7 days at 25°C and 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 normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

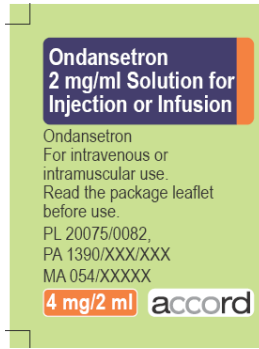


Module 4 Labelling

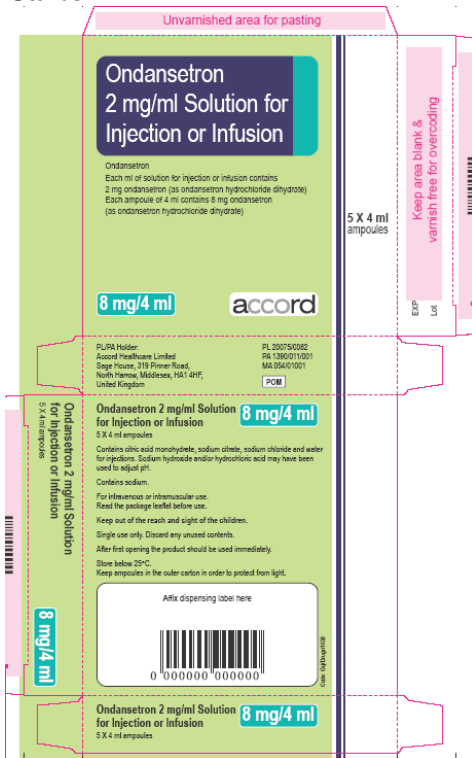
Ondansetron 2mg/ml Solution for Injection Carton

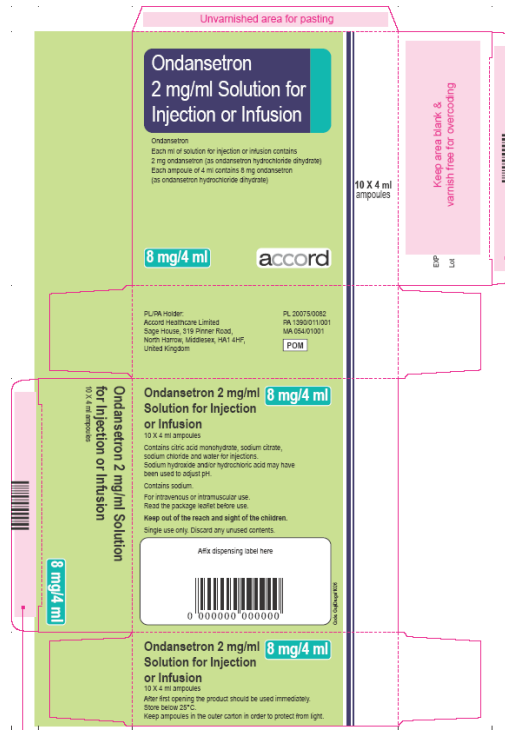


Label

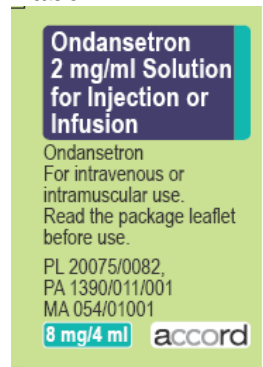


Carton





Label



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Ondansetron 2mg/ml Solution for Injection, in the management of nausea or vomiting as a result of cancer chemotherapy/radiotherapy, and for the prevention of post-operative nausea and vomiting in adults and children, is approvable.

This is an application submitted under Article 10(1) of Directive 2001/83 (as amended) for Ondansetron 2mg/ml Solution for Injection. It has been shown to be a generic medicinal product of the originator product Zofran Injection 2mg/ml (Marketing Authorisation Holder: GlaxoSmithKline) which was first registered on 8th January 1991 (The Netherlands); hence the 10 year rule is fulfilled.

The product contains the active ingredient ondansetron, a potent, highly selective serotonin (5HT₃) receptor antagonist. The 5HT₃ antagonists are a class of medications which act as receptor antagonists at the 5-hydroxytryptamine-3 receptor (5HT₃ receptor), a subtype of serotonin receptor found in terminals endings of the vagus nerve and in certain areas of the brain. Most 5HT₃ antagonists are antiemetics, used in the prevention and treatment of nausea and vomiting.

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. 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.

The application is in accordance with Article 10(1) of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

A formal *Environment Assessment* was not submitted. This is acceptable as no increase in environmental risk is to be expected compared to that of the reference product.

No *Risk Management Plan* other than the documentation of the PharmacoVigilance system has been provided. This is acceptable for generics, since the innovator product is not subject to specific risk management procedures.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

Since a literature review has been presented for the Non-clinical Overview, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

No new clinical study was submitted.

The 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 upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Ondansetron 2mg/ml Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Ondansetron (as hydrochloride dihydrate)
Pharmacotherapeutic classification (ATC code)	Serotonin (5HT ₃) antagonists (A04AA)
Pharmaceutical form and strength(s)	2mg/ml Solution for Injection or Infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/1250/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Finland, Hungary, Ireland, Italy, Latvia, Malta, Norway, Poland, Portugal, Sweden, Slovenia, Slovak Republic and Spain.
Marketing Authorisation Number(s)	PL 20075/0082
Name and address of the authorisation holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, Harrow, Middlesex HA1 4HF UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Ondansetron

General Information

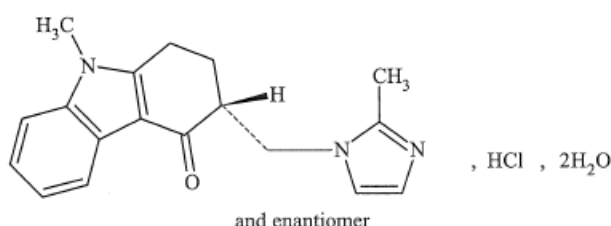
Nomenclature

Name: Ondansetron hydrochloride dihydrate (INN: Ondansetron)

Chemical name:

- 4H-carbazol-4-one, -1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-, monohydrochloride, (\pm)-, dihydrate.

Structure



Molecular formula: $C_{18}H_{19}N_3O.HCl.2H_2O$

Molecular weight: 365.9

General Properties

White or almost white powder.

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

There is a Ph Eur monograph for the drug substance, Ondansetron hydrochloride dihydrate.

Manufacture

A satisfactory Ph Eur Certificate of Suitability (CEP) has been provided which covers the manufacture and control of the active drug substance ondansetron.

An appropriate specification is provided for the active substance ondansetron. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active ondansetron is stored in appropriate packaging that complies with Directive 2002/72/EC (as amended) and is suitable for contact with foodstuffs. The specifications and typical analytical test reports are provided and are satisfactory. Specifications and Certificates of Analysis have been provided.

Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for standards used by the active substance manufacturer during validation studies.

The finished product manufacturer routinely tests each batch of the drug substance in accordance with the following specification upon receipt.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely citric acid monohydrate, sodium citrate, sodium chloride, sodium hydroxide (pH adjustment), hydrochloric acid concentrated (pH adjustment) and water for injections. An appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph.Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

There were no novel excipients used and no overages.

Pharmaceutical Development

The objective of development activities was to achieve a stable formulation of ondansetron hydrochloride 2mg/ml that is similar to the innovator product Zofran, manufactured by GlaxoSmithKline S.p.A.

Essential Similarity

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. The physico-chemical properties of the drug product have been compared with the originator product. Comparative impurity profiles have been provided for the finished product versus the reference product Zofran 2mg/ml Solution for Injection (GlaxoSmithKline UK).

Compatibility

An in-house study was performed to assess the compatibility of Ondansetron 2mg/ml Injection with various intravenous fluids.

The compatibility profile was demonstrated to be the same as that described for the originator product.

Manufacture

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

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. In-process controls are appropriate considering the nature of the product and the method of manufacture. The manufacturing process has been validated on three pilot scale batches of the 2ml product and three pilot-scale batches of the 4ml product and has been shown to be satisfactory results.

Finished product specification

The finished product specification 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 working standards used.

Container Closure System

The product is packaged in ampoules composed of Type I clear glass. Specifications and Certificates of Analysis for all the packaging used have been provided. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food. The product is packaged in sizes of 2ml or 4ml ampoules packed in cartons holding either 10 or 5 ampoules each. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Stability

Stability studies were performed on six pilot scale batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years for an unopened product with storage conditions “Store below 25°C” and “Keep ampoules in the outer carton in order to protect from light”.

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set (After dilution with recommended diluents chemical and physical in-use stability has been demonstrated for 7 days at 25°C and 2-8°C), which is satisfactory. The precautions “Store below 25°C” and “Keep ampoules in the outer carton in order to protect from light” are considered acceptable.

Regarding the shelf-life of the injection “Once opened, the product should be used immediately”.

Storage conditions for the infusion are “Chemical and physical in-use stability has been demonstrated for 7 days at 25°C and 2-8°C with the solutions given in section 6.6 of the SmPC”.

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

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are pharmaceutically acceptable.

MAA form

The MAA form is pharmaceutically acceptable.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron are well known. As ondansetron is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by a suitably qualified person. The Non-clinical Overview contains a review of 39 references up to 2007.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Assessor's comment:

The product is a straightforward injectable formulation and there are no issues arising from the impurities or residual solvents.

Conclusions

There are no objections to approval of Ondansetron 2 mg/ml Injection from a non-clinical point of view.

III.3 CLINICAL ASPECTS INTRODUCTION

Introduction

The clinical overview has been written by a suitably qualified person. The report refers to 53 publications up to year 2006.

Assessor's comment: The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Clinical study reports

No clinical studies have been submitted.

Assessor's comment: Given that this is a generic parenteral formulation of ondansetron hydrochloride no clinical studies are required.

Biowaiver

Assessor's comment:

In accordance with CPMP/EWP/QWP/1401/98 section 5.1.6 Parenteral solutions: As the proposed generic involves the same type of solution (i.e. aqueous), the same concentration of the same active substance and comparable excipients as the reference product, no bioequivalence testing for the proposed IM/IV route is required.

Pharmacokinetic studies

None have been conducted and none are required for this application.

Pharmacodynamic studies

None have been conducted and none are required for this application.

Additional data

N/A

Post marketing experience

No post-marketing data is available. The medicinal product has not been marketed in any country.

Ondansetron hydrochloride has a well-recognised efficacy and an acceptable level of safety in the indications approved for Zofran Injection 2mg/ml (GSK) and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

Summary of Product Characteristics

This is satisfactory.

Patient Information Leaflet

This is satisfactory.

Benefit-Risk assessment

The application contains an adequate review of published clinical data and given that this is a parenteral preparation and bioequivalence testing is not required, approval is recommended from the clinical point of view.

CONCLUSIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.

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OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ondansetron 2mg/ml Solution for Injection is 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 applications of this type.

EFFICACY

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that 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. Extensive clinical experience with ondansetron hydrochloride dihydrate 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