

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 2mg ondansetron as ondansetron hydrochloride dihydrate and contains 3.56 mg of sodium as sodium citrate and sodium chloride.

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

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

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Glass amber ampoule containing a colourless 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 after dilution for intravenous infusion.

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 and selected as shown below.

Emetogenic chemotherapy and radiotherapy

For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by oral or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron should initially be administered intravenously immediately before treatment, followed by 8 mg orally twelve hourly.

For oral administration: 8 mg 1-2 hours before treatment, followed by 8 mg 12 hours later.

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. The recommended dose for oral administration is 8 mg twice daily.

Highly emetogenic chemotherapy

Adults: Either 8 mg as a slow intravenous bolus injection or as a short-term infusion lasting 15 minutes immediately before chemotherapy. If this initial dose has insufficient effect it can be supplemented by either 8 mg (intravenous bolus or 15 minutes' infusion) every 4th hour, at most twice, or continuous infusion of 1 mg/hour for 24 hours. In some cases the initial dose can be increased to 32 mg diluted with a compatible infusion fluid as an infusion lasting at least 15 minutes immediately before chemotherapy.

After 24 hours treatment is changed to the oral route.

The effect of ondansetron may be enhanced by the simultaneous administration of 20 mg dexamethasone intravenously or an equally potent dose of other glucocorticoids for intravenous use.

Children (aged 2 years and over) 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 minutes immediately before chemotherapy, followed by 4 mg orally twelve hours later. Oral treatment with a dose according to the body area should be continued for up to 5 days after a course of treatment. Children with a total body area between 0.6 and 1.2 m² should receive a dosage schedule of 4 mg 3 times a day, while children with a body area above 1.2 m² should receive 8 mg 3 times a day.

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

Ondansetron solution for injection cannot be used in children with a total body surface below 0.6 m².

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".

Post-operative nausea and vomiting (PONV)

Prevention of PONV

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

Adults: 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 SPC of ondansetron tablets.

Children aged 2 years and over: 0.1 mg/kg up to a maximum of 4 mg as a slow intravenous bolus injection either before, at or after induction of anaesthesia.

Treatment of established PONV

For the treatment of established PONV a single dose of 4-8 mg given by slow intravenous injection is recommended.

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

For the prevention and treatment of PONV slow intravenous injection is recommended.

0.1 mg/kg up to a maximum of 4 mg as a slow intravenous bolus injection

Elderly

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting (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 medicinal product 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 5-HT₃-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 5-HT₃ receptor antagonists.

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

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.

Since 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 solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium-free'.

Ondansetron solution for injection should not be used in children with a total body surface below 0.6 m².

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

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicinal products commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, propofol and thiopental.

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

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

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

4.6 Pregnancy and lactation

Pregnancy

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. Use in human pregnancy has not been established and 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 (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

Ondansetron 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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($< 1/10,000$) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

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

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures.

Rare: Dizziness during rapid intravenous 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

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. Local burning sensation following insertion of suppositories.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests.

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

General disorders and administration site conditions

Common: Local intravenous. injection site reactions

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT₃) antagonists

ATC Code: A04AA01

Ondansetron is a potent, highly selective 5-HT₃ receptor-antagonist.

Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT₃ 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

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

The disposition of ondansetron following oral 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.

The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 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 100ml/min 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 normalizing systemic exposure in paediatric patients.

In patients with moderate renal impairment (creatinine clearance 15-60ml/min), both systemic clearance and volume of distribution are reduced, 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 oral or intravenous 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.

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, 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

Sodium Chloride
Citric Acid Monohydrate.
Sodium Citrate.
Water for injections.

6.2 Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication except the recommended infusion diluents mentioned in section 6.6.

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

6.3 Shelf Life

Unopened 3 years.

After first opening the Injection':

The product should be used immediately after opening. The injection is intended for single-dose use only with any remaining solution discarded immediately after initial use.

After dilution for intravenous infusion:

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 reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user

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

6.5 Nature and contents of container

Amber glass ampoules, type 1, containing 2 ml or 4 ml solution

Packs of 5 and 5 x 5 ampoules.

Not all pack sizes may be marketed.

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

Injection:

For single use only. Any unused solution should be discarded.

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

Infusion:

May be diluted with solution for infusion containing: sodium chloride 9 mg/ml (0.9%), glucose 50 mg/ml (5 %), mannitol 100 mg/ml (10 %) potassium chloride 3 mg/ml (0.3%)+ sodium chloride 9 mg/ml (0.9 %) and potassium chloride 3 mg/ml (0.3%) + glucose 50 mg/ml (5 %) as well as Ringer solution for infusion.

Should not be mixed with other pharmaceutical products.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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