Ondansetron 2 mg/2ml – 2 mg/4ml Solution for Injection

Each ampoule with 2 ml contains 4 mg ondansetron.
Each ampoule with 4 ml contains 8 mg ondansetron.

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

Paediatric Population: Ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of PONV in children aged ≥1 month.

Dose 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.

hemotherapy 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 dose range of ondansetron solution for injection or infusion is 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy: For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by intravenous or other routes of administration, however this product is for intravenous use only.

The recommended intravenous dose of ondansetron is 8 mg administered as a slow injection (in not less than 30 seconds) or as an infusion over 15 minutes immediately before treatment, followed by treatment with dosage forms other than intravenous. Treatment with dosage forms other than intravenous is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given by intravenous or other routes of administration, however this product is for intravenous use only.

Ondansetron has been shown to be equally effective in the following intravenous dose schedules over the first 24 hours of chemotherapy:

• A single dose of 8 mg by slow intravenous injection (in not less than 30 seconds) immediately before chemotherapy.
• A dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or as a short-time intravenous infusion over 15 minutes immediately before chemotherapy, followed by two further intravenous doses of 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.
• A maximum initial intravenous dose of 16 mg diluted in 50-100 ml of sodium chloride 9 mg/ml (0.9 % w/v) solution 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. The initial dose of Ondansetron may be followed by two additional 8 mg intravenous doses (in not less than 30 seconds) four hours apart. A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk. (see sections 4.4, 4.8 and 5.1)

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, ondansetron treatment with dosage forms other than intravenous should be continued after a course of treatment.

Paediatric Population: CINV in children aged ≥ 6 months and adolescents

The dose for CINV 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).

Ondansetron injection should be diluted in 5% glucose or 0.9% sodium chloride or other compatible infusion fluid (see section 6.6) and infused intravenously over not less than 15 minutes. There are no data from controlled clinical trials on the use of Ondansetron in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of Ondansetron 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 (Table 1).
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. plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0.6 m^2	5 mg/m^2 i.v. plus 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs

- The intravenous dose must not exceed 8mg.
- 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 (Table 2).
Table 2: Weight-based dosing for Chemotherapy - Children aged ≥6 months and adolescents

Weight	Day 1 [a,b]	Days 2-6[b]
≤ 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	2 mg syrup every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	4 mg syrup or tablet every 12 hrs

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

Elderly
In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart (see section 5.2).

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

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

Paediatric population: PONV in children aged ≥ 1 month and adolescents: 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 of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For the treatment of PONV after surgery 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 of 0.1 mg/kg up to a maximum of 4 mg. There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

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

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

Contraindications
Hypersensitivity to the active substance or to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients listed in section: Sodium chloride, Sodium citrate dihydrate, Citric acid monohydrate, Water for injections.

Concomitant use with apomorphine Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias (see section 4.4).

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs) (see section 4.4).

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Interactions
Effects of ondansetron on other medicinal products

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

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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias (see section 4.4).

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs) (see section 4.4).

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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.

Special warnings and precautions for Section - 4.4
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

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

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

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.

Paediatric Population: Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

CINV: When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/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 comparison indicates similar efficacy for both regimens (section 5.1).

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

Undesirable side effects - Section 4.8
The following frequency terminology is used: very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100;

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 receptor antagonists.

Nervous system disorders: Very common: Headache.

Rare: Dizziness during rapid intravenous administration.
Rare: Transient visual disturbances (e.g. blurred vision) during rapid intravenous administration.

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

Rare: Transitory changes in the electrocardiogram, QTc prolongation (including Torsades de Pointes)

Vascular disorders: Common: Sensations of flushing or warmth.

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

General disorders and administration site conditions: Common: Local reactions at the IV injection site

Pharmacodynamic properties – section 5.1
Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist:I ts precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations. The role of ondansetron in opiate-induced emesis is not yet established: The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested

dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Paediatric population: CINV: 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 (S3AB3006). On the days of chemotherapy, patients received either Ondansetron 5 mg/m2 intravenous + ondansetron 4 mg orally after 8-12 hrs or ondansetron 0.45 mg/kg intravenous + placebo orally after 8-12 hrs. 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% (5 mg/m2 intravenous + ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous + placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients 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 5 mg/m2 intravenous together with 2-4 mg dexamethasone orally

• 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2-4 mg dexamethasone orally 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 openlabel, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 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-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 yrs and 8 mg for children aged ≥ 12 yrs (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

PONV: 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). Included subjects were scheduled to undergo elective 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).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735)) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3: Prevention and treatment of PONV in Paediatric Patients – Treatment response over

Study	Endpoint	Ondansetron %	Placebo %	p value
S3A380	CR	68	39	≤ 0.001
S3GT09	CR	61	35	≤ 0.001
S3A381	CR	53	17	≤ 0.001
S3GT11	no nausea	64	51	0.004
S3GT11	no emesis	60	47	0.004

Special precautions for disposal and other handling - section 6.6.
The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

- Sodium chloride 9 mg/ml (0.9 % w/v) solution
- Glucose 50 mg/ml (5 % w/v) solution
- Mannitol 100 mg/ml (10 % w/v) solution
- Ringer's lactate solution

The diluted solutions should be stored protected from light.
Note: The solution for injection must not be sterilized in an autoclave
Pregnancy and lactation
Women of childbearing potential: Women of childbearing potential should consider the use of contraception.

Pregnancy:
Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However Ondansetron should not be used during the first trimester of pregnancy.

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

How to store
For those genes, there are special conditions to be met.