DIRECTIONS FOR USE

B. Braun Melsungen AG, 34209 Melsungen, Germany

NAME OF THE MEDICINAL PRODUCT

Ondansetron B. Braun 2 mg/ml solution for injection or infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 2 mg ondansetron as ondansetron hydrochloride dihydrate
Each ampoule with 2 ml contains 4 mg ondansetron.

Excipient with known effect:
1 ml solution for injection or infusion contains 3.34 mg of sodium as sodium citrate dihydrate and sodium chloride.

For a full list of excipients, see section *Pharmaceutical Particulars*.

PHARMACEUTICAL FORM

Solution for injection or infusion

Clear and colourless aqueous solution

CLINICAL PARTICULARS

Indications

Adults
Ondansetron B. Braun 2 mg/ml solution for injection or infusion is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Ondansetron B. Braun 2 mg/ml solution for injection or infusion is also indicated for the prevention and treatment of post-operative nausea and vomiting
Paediatric population
Ondansetron B. Braun 2 mg/ml solution for injection or infusion is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy
Ondansetron B. Braun 2 mg/ml solution for injection or infusion is also indicated for the prevention and treatment of postoperative nausea and vomiting

Dosage and Administration

Ondansetron is available for oral and parenteral use to allow the route of administration and dosing to be flexible. However this product is for intravenous or intramuscular use only.

Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV)
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

- **CINV and RINV in Adults**

The recommended intravenous (IV) or intramuscular (IM) dose of ondansetron is 8 mg administered immediately before treatment.

- Highly emetogenic chemotherapy

A single dose of ondansetron 8 mg by slow intravenous injection immediately before chemotherapy has been shown to be effective in many patients. For highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given due to dose- dependent increase of QT prolongation risk (see Warnings and Precautions, Adverse Reactions, Pharmacodynamic Effects).

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

IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes (see *Special precautions for disposal and other handling*).
Ondansetron doses of 8 mg ondansetron or less, do not need to be diluted and may be administered as a slow IM or IV injection in not less than 30 seconds.

The initial dose of Ondansetron B. Braun may be followed by 2 additional IV or IM doses of 8 mg no less than four hours apart.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

- **CINV in children and adolescents (aged 2 years and over)**

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. Ondansetron injection should be diluted in 5 % glucose or 0.9 % sodium chloride or other compatible infusion fluid 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 in children. 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/m^2.
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).

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥ 2 years and adolescents

BSA	Day 1[(a)]	Days 2-6
0.6 m^2 - 1.2 m^2	5 mg/m^2 i.v. plus 4 mg oral liquid or tablet after 12 hrs.	4 mg oral liquid formulation or tablet every 12 hrs.

a The intravenous dose must not exceed 8 mg.

- **CINV and RINV in Elderly**

In patients 65 to 74 years of age, the initial IV dose of Ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart. All IV doses should be diluted in 50 – 100 mL of saline or other compatible infusion fluid and infused over 15 minutes.

In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg, infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart (see *Special Patient Population, Elderly*). All IV doses should be diluted in 50 – 100 mL of saline or other compatible infusion fluid and infused over 15 minutes.

- **Renal impairment**

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

- **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 not different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

POST-OPERATIVE NAUSEA AND VOMITING

- **PONV in Adults**

For the prevention of post-operative nausea and vomiting, the recommended dose of ondansetron is a single dose of 4 mg by IM or slow IV injection administered at the induction of anaesthesia.

For treatment of established post-operative nausea and vomiting a single dose of 4 mg given by IM or slow IV injection is recommended.

- **PONV in Children and Adolescents (aged 2 years and over)**

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow IV 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, or after surgery.

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

- **Elderly**

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly. However ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

- **Renal Impairment**

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

- **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 not different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

Contraindications

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

Hypersensitivity to any components of the preparation.

Warnings and Precautions

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.
Ondansetron prolongs the QT interval in a dose-dependent manner (see *Pharmacodynamic Effects*). 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, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. Therefore, caution should be exercised in patients with cardiac rhythm or conduction distrubances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

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.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been described following the concomitant use of ondansetron and other serotonergic drugs (see *Interactions*). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

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.
This medicinal product contains 2.3 mmol (or 53.5 mg) sodium per maximum daily dose of 32 mg. To be taken into consideration by patients on a controlled sodium diet.

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

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

Interactions

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it.
Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with:

- alcohol
- temazepam
- furosemide
- alfentanil
- tramadol (metabolism)
- propofol
- 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.

Use of ondansetron with QT prolonging drugs and/or drugs that cause electrolyte abnormalities may result in additional QT prolongation.
Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. Therefore, caution should be exercised when ondansetron is co-administration with drugs that prolong the QT interval and /or cause electrolyte abnormalities and/or cardiotoxic drugs (see *Warnings and Precautions*).

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, Carbamazepin 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.

Serotonergic drugs (including SSRIs and SNRIs)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see *Warnings and Precautions*).

Tramadol
Tramadol partly exerts its analgetic effects via a serotonin dependant mechanism. As ondansetron is a 5HT3 receptor antagonist an influence on the analgetic potential is suspected. Additionally, data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

Pregnancy and Lactation

Risk Summary
In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy (see Human data). Regarding cardiac malformations the epidemiological studies showed conflicting results.
The use of ondansetron in pregnancy is not recommended.
Human Data
Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy.
One cohort study with 88,467 ondansetron exposed pregnancies showed an increased risk of oral clefts (3 additional cases per 10, 000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations.
One case-control study using population-based birth defect registries with 23,200 cases across two datasets reported an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study.
The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95% CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations, adjusted RR 1.3 (95% CI 0.86-1.8).
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.

Effects on Ability to Drive and use Machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

Adverse Reactions
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (frequency cannot be estimated from the available data), 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 form post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron. The adverse event profiles in children and adolescents were comparable to that seen in adults.

Immune system disorders
Rare: Immediate hypersensitivity reactions, sometimes severe including anaphylaxis.

Nervous system disorders
Very common: Headache
Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia) have been observed without definitive evidence of persistent clinical sequelae,
Rare: Dizziness predominantly during rapid IV administration

Psychiatric disorders
Very rare: Depression

Eye disorders
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare: Transient blindness predominantly during IV 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. Cardiac arrhythmias may be fatal in isolated cases.
Rare: QTc prolongation (including Torsade de Pointes).
Not known: Myocardial ischemia (see *Warnings and Precautions*).

Vascular disorders
Common: Sensations of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thorax and mediastinum disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Constipation.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests.

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

Skin and subcutaneous tissue disorders
Uncommon: Hypersensitivity reactions around the administration site (e.g. rash, urticaria, itching).
Very rare: Toxic skin eruption, including toxic epidermal necrolysis.

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

Note
Patients should inform their doctor if they notice any of these reactions or other adverse reactions.

Overdose
Symptoms and Signs
There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see *Adverse Reactions*). 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.

Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Cases consistent with serotonin syndrome have been reported in young children following oral overdoses

Treatment
There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The use of ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of action
Ondansetron is a potent, highly selective $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ 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.

Pharmacodynamic effects
Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
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.

Pharmacokinetics

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Absorption
Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

Distribution
Ondansetron is not highly protein bound (70-76%).
The disposition of ondansetron following oral, IM or IV dosing in adults is similar with a steady state volume of distribution of about 140 L.

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.

Elimination
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine. The disposition of ondansetron following oral, IM or IV dosing is similar with a terminal elimination half life is about 3 hours.

Special Patient Populations

- **Gender**

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).

- **Children and Adolescents (aged 2 years and over)**

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.

- **Elderly**

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see Dosage and Administration – CINV and RINV in Elderly).

- **Renal impairment**

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

- **Hepatic impairment**

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.

Pre-Clinical Safety Data

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see *Pharmacodynamic Effects - QT prolongation*).

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium chloride
Sodium citrate dihydrate
Citric acid monohydrate
Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section *Special precautions for disposal and other handling*.

Shelf life

– unopened:
36 months

– after first opening the container
Not applicable. See section *Special precautions for disposal and other handling*.

– after dilution (infusion)
Not more than 24 hours at 2 - 8°C with the solutions given in section *Special precautions for disposal and other handling.*

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.

The diluted solutions should be stored protected from light.

Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.
Do not store above 30°C.

For storage conditions of the diluted medicinal product, see section *Shelf life*.

Nature and contents of container

Ampoules of colourless glass type I (Ph. Eur.), contents: 2 ml
Pack sizes
5 x 2 ml, 10 x 2 ml

Not all pack sizes may be marketed.

Special precautions for disposal and other handling

For single use only. After use discard container and any remaining contents.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.
The product should be used immediately after opening the container.
Any unused product or waste material should be disposed of in accordance with local requirements.

<u>Dilution</u>
Ondansetron 2 mg/ml may be diluted with the following solutions for infusion:
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

MARKETING AUTHORISATION NUMBER

SIN Reg. no: SINXXXXXP

DATE OF REVISION OF THE TEXT

04.2022

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