[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.
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.
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.
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.
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 0.1mg/kg up to a maximum of 4mg.
There are no data on the use of Ondansetron Injection USP 2 mg/ml 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.

Use immediately upon opening.
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 below 30°C, protected from light.
Any unused product or waste material should be disposed of in accordance with local requirements.

PRESENTATION:
ONDARON: 5 ampoules are then packed in blister pack. Such One blister pack is packed in a carton along with pack insert.

STORAGE:
Store at a temperature between 20 and 30C. Protected from light.
5 Ampoules are packed in a tray pack. Such 1 tray is packed in a carton along with package insert.

Keep out of reach of children.

SHELF LIFE:
24 months from the date of Manufacturing.

Manufactured for
BETA PHARMA LABORATUVAR ILAÇ SAN .VE TİC .LTD .ŞTİ
MOLLA GURANI MAH. TURGUT OZAL MILLET
CADNO:84/201 FATIH/ ISTANBUL TURKIYE

℞
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ONDARON 8

Ondansetron Injection
For IV/IM Use

DESCRIPTION:
Ondansetron hydrochloride (HCl) is the racemic form of Ondansetron and a selective blocking agent of the serotonin 5-HT3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. The empirical formula is $C_{18}H_{19}N_3OHCl2H_2O$, representing a molecular weight of 365.86. Ondansetron HCl is a white to off-white powder that is soluble in methanol; sparingly soluble in water, in dichloromethane and in Ethanol.

DOSAGE FORM: Injection

COMPOSITION:
Each ml Contains:
Ondansetron Hydrochloride
Equivalent to Ondansetron ……2 mg
Water for Injections BP…….. q.s.

PRODUCT DESCRIPTION: Clear colourless liquid

PHARMACOLOGICAL CLASSIFICATION: Highly selective $5HT_3$ receptor-antagonist.

PHARMACOLOGICAL ACTIONS:
Mechanism of action:
Ondansetron is a selective serotonin 5-HT_3 receptor antagonist. The antiemetic activity of the drug is brought about through the inhibition of 5-HT_3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT_3 receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone.

Pharmacodynamics
Ondansetron is a highly specific and selective serotonin 5-HT_3 receptor antagonist, not shown to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serontonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery, and centrally in the chemoreceptor trigger zone of the area postrema. The temporal relationship between the emetogenic action of emetogenic drugs and the release of serotonin, as well as the efficacy of antiemetic agents suggest that chemotherapeutic agents release serotonin from the enterochromaffin cells of the small intestine by causing degenerative changes in the GI tract. The serotonin then stimulates the vagal and splanchnic nerve receptors that project to the medullary vomiting center, as well as the 5-HT_3 receptors in the area postrema, thus initiating the vomiting reflex, causing nausea and vomiting.

Pharmacokinetics
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.
Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (five 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).
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 mg/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.

INDICATIONS & USAGE
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.

CONTRAINDICATION
Hypersensitivity to ondansetron or to other selective $5HT_3$ receptor antagonists (e.g. Granisetron, dolasetron) or to any of the excipients.
The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

WARNINGS
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.
Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitive reactions.
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.
As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration
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.
Paediatric Population:
Paediatric population receiving ondansetron with hepatotoxic chemotherapeutical agents should be monitored closely for impaired hepatic function.
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/m^2 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.

DRUG INTERACTIONS
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, tramadol, morphine, lidocaine, propofol, alfentanil or thiopental.
Tramadol
Data from small studies indicate that ondansetron may reduce the analgestic 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.
Apomorphine: Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated.
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.

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 pre- 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.

ADVERSE REACTIONS:
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) not known (cannot be estimated from the available 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. Anaphylaxis may be fatal.
Cross-sensitivity has also been observed in patients who are hypersensitive to other selective $5HT_3$ antagonists.
Nervous system disorders
Very common:Headache.
Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia), observed without definitive evidence of persistent clinical sequelae.Rare: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.*General disorders and administration site conditions*Common:local intravenous site reactions (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

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

OVERDOSAGE
Symptoms and Signs
Little is known at present about overdosage with ondansetron; however, a limited number of patients received overdoses. . In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.
Treatment
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.
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.

DOSAGE AND ADMINISTRATION
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 immediately before treatment, followed by 8 mg orally twelve hourly.
To protect against delayed or prolonged emesis after the first 24 hours, oral 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 and over not less than 15 minutes immediately before chemotherapy.
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 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.
Ondansetron hydrochloride should be diluted in 5% dextrose 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 Injection USP 2 mg/ml 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/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. 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 tablet after 12 hours	4 mg syrup or tablet every 12 hours