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

Ondansetron Injection IP

Ondacool*

2 mg / ml

For intramuscular and intravenous use

Composition:
Each ml contains:
Ondansetron Hydrochloride IP
equivalent to Ondansetron ..... 2 mg
Methyl Paraben (As preservative) IP ..... 0.18 % w/v
Propyl Paraben (As preservative) IP ..... 0.02 % w/v
Water for Injections IP ..... q.s.

Dosage form and strength
Injection (2mg)

Clinical particulars
Therapeutic indication
In the treatment and management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Posology and method of administration.
Posology:

Adults
The recommended adult intravenous dosage of ondansetron is three 0.15mg/kg doses up to a maximum of 16 mg per dose. The first dose is infused over 15 minutes, beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron.

Paediatric Use
For paediatric patients (6 months through 18 years of age), the intravenous dosage of ondansetron is three 0.15mg/kg doses up to a maximum of 16 mg per dose. The first dose is to be administered 30 minutes before the start of moderately-to-highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron. The drug should be infused intravenously over 15 minutes.

Method of Administration: Administered through an IV line
The recommended dosage for adult and pediatric patients 6 months of age and older for prevention of nausea and vomiting associated with chemotherapy is 0.15-mg/kg per dose for 3 doses (maximum of 16 mg per dose).
Caution: Dilution of ondansetron injection is required in adult and pediatric patients prior to administration.
The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used. Do not use if container is damaged.

Contraindications
Ondansetron injection is contraindicated for patients known to have hypersensitivity (e.g., anaphylaxis) to this product or any of its components. Anaphylactic reactions have been reported in patients taking ondansetron.

Special warnings and precautions for use
Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.
QT Prolongation
Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, postmarketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron injection in patients with congenital long QT syndrome. Electrocardiogram (ECG) monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.
Serotonin Syndrome
The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of ondansetron injection alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.
Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of ondansetron injection and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue ondansetron injection and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ondansetron injection is used concomitantly with other serotonergic drugs.
Myocardial Ischemia
Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms appeared immediately after administration but resolved with prompt treatment. Coronary artery spasm appears to be the most common underlying cause. Therefore, do not exceed the recommended infusion rate of ondansetron injection and monitor patients for signs and symptoms of myocardial ischemia during and after administration.

Masking of Progressive Ileus and Gastric Distension
The use of ondansetron injection in patients following abdominal surgery or in patients with chemotherapy induced nausea and vomiting may mask a progressive ileus and gastric distension. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. Ondansetron injection is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

Drugs interactions
Drugs Affecting Cytochrome P-450 Enzymes
Ondansetron does not appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of limited available data, no dosage adjustment is recommended for patients on these drugs.

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.

Phenytoin, Carbamazepine, and Rifampin
In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

Tramadol
Although there are no data on pharmacokinetic drug interactions between ondansetron and tramadol, data from two small trials indicate that concomitant use of ondansetron may result in reduced analgesic activity of tramadol. Patients on concomitant ondansetron self-administered tramadol more frequently in these trials, leading to an increased cumulative dose in patient-controlled administration of tramadol.

Serotonergic Drugs
Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including SSRIs and SNRIs.

Chemotherapy
In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron. In a crossover trial in 76 pediatric patients, intravenous ondansetron did not increase blood levels of high-dose methotrexate.

Temazepam
The co-administration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.
Alfentanil and Atracurium
Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

Use in special populations (such as pregnant women, lactating women, Paediatric patients, geriatric patients etc.)
Pregnancy
Risk Summary
Published epidemiological studies on the association between ondansetron use and major birth defects have reported inconsistent findings and have important methodological limitations that preclude conclusions about the safety of ondansetron use in pregnancy (see Data). Available postmarketing data have not identified a drug-associated risk of miscarriage or adverse maternal outcomes. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered intravenously during organogenesis at approximately 3.6 and 2.9 times the maximum recommended human intravenous dose of 0.15 mg/kg given three times a day, based on body surface area (BSA), respectively (see Data).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriages, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Human Data
Available data on ondansetron use in pregnant women from several published epidemiological studies preclude an assessment of a drug-associated risk of adverse fetal outcomes due to important methodological limitations, including the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, recall bias, and other unadjusted confounders.

Ondansetron exposure in utero has not been associated with overall major congenital malformations in aggregate analyses. One large retrospective cohort study examined 1970 women who received a prescription for ondansetron during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage, stillbirth, preterm delivery, infants of low birth weight, or infants small for gestational age.

Animal Data
In embryo-fetal development studies in rats and rabbits, pregnant animals received intravenous doses of ondansetron up to 10 mg/kg/day and 4 mg/kg/day, respectively, during the period of organogenesis. With the exception of short periods of maternal weight loss and a slight increase in the incidence of early uterine deaths at the high dose level in rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 10 mg/kg/day in rats and 4 mg/kg/day in rabbits, the maternal exposure margin was approximately 3.6 and 2.9 times the maximum recommended human oral dose of 0.15 mg/kg given three times a day, respectively, based on BSA.

No intravenous pre- and post-natal developmental toxicity study was performed with ondansetron. In an oral pre- and post-natal development study pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation.

Lactation
Risk Summary
It is not known whether ondansetron is present in human milk. There are no data on the effects of ondansetron injection on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ondansetron injection and any potential adverse effects on the breast-fed infant from ondansetron injection or from the underlying maternal condition.

Pediatric Use
Little information is available about the use of ondansetron in pediatric surgical patients younger than 1 month. Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months.

The clearance of ondansetron in pediatric patients aged 1 month to 4 months is slower and the half-life is ~2.5fold longer than patients who are aged > 4 to 24 months. As a precaution, it is recommended that patients younger than 4 months receiving this drug be closely monitored.

Geriatric Use
Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting US- and foreign-controlled clinical trials, 862 were aged 65 years and older. No overall differences in safety or effectiveness were observed between subjects 65 years and older and younger subjects. A reduction in clearance and increase in elimination half-life were seen in patients older than 75 years compared with younger subjects. There were an insufficient number of patients older than 75 years of age and older in the clinical trials to permit safety or efficacy conclusions in this age-group. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65.

Hepatic Impairment
In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

Renal Impairment
Although plasma clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 mL/min), no dosage adjustment is recommended.

Effects on ability to drive and use machines
Driving and use of machines
Ondansetron Injection should not affect your ability to drive or use machines. However, if any of the side effects affect you (e.g. dizziness, blurred vision) caution is advisable. Do not drive or operate if you are feeling unwell.

Undesirable effects
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Hypersensitivity Reactions
- QT Prolongation
- Serotonin Syndrome
- Myocardial Ischemia
- Masking of Progressive Ileus and Gastric Distension

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse reactions have been reported in clinical trials of adult patients treated with ondansetron, the active ingredient of intravenous ondansetron injection across a range of dosages. A causal relationship to therapy with ondansetron injection (ondansetron) was unclear in many cases.
Cardiovascular: Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported.

Gastrointestinal: Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.

Hepatic: In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur.

Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.

Neurological: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron injection, and rare cases of grand mal seizure.
Other: Rare cases of hypokalemia have been reported.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of ondansetron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron.

Cardiovascular
Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope. Rarely and predominantly with intravenous ondansetron, transient ECG changes, including QT/QTc interval prolongation have been reported.

Myocardial ischemia was reported predominately with intravenous administration

General
Flushing: Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported. A positive lymphocyte transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

Hepatobiliary
Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications, including potentially hepatotoxic cytotoxic chemotherapy and antibiotics.

Local Reactions
Pain, redness, and burning at site of injection.
Lower Respiratory
Hiccups.

Neurological
Oculogyric crisis, appearing alone, as well as with other dystonic reactions. Transient dizziness during or shortly after intravenous infusion.

Skin
Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Eye Disorders
Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours. Transient blurred vision, in some cases associated with abnormalities of accommodation, has also been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

Overdose
There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse reactions listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48 mg of ondansetron hydrochloride tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

Pharmacological properties

Mechanism of Action
Ondansetron is a selective 5-HT3 receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist.

Pharmacodynamic properties
In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another trial in 6 normal male volunteers, a 16 mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or ECG. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations. In a gender balanced pharmacodynamic trial (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the ipecacuanha model of emesis.

Cardiac Electrophysiology
QTc interval prolongation was studied in a double-blind, single intravenous dose, placebo- and positivecontrolled, crossover trial in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 19.5 (21.8) ms and 5.6 (7.4) ms after 15-minute intravenous infusions of 32 mg and 8 mg ondansetron injection, respectively. A significant exposure-response relationship was identified between ondansetron concentration and ΔΔQTcF. Using the established exposure-response relationship, 24 mg infused intravenously over 15 minutes had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) ms. In contrast, 16 mg infused intravenously over 15 minutes using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) ms. In this study, the 8-mg dose infused over 15 minutes did not prolong the QT interval to any clinically relevant extent.

Pharmacokinetic properties
Absorption
A trial was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a single 4-mg dose administered as a 5-minute infusion compared with a single intramuscular injection. Systemic exposure as measured by mean area under curve (AUC) were equivalent, with values of 156 [95% CI 136, 180] and 161 [95% CI 137, 190] ng•h/mL for intravenous and intramuscular groups, respectively. Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/mL at 10 minutes after intravenous infusion and 31.9 [95% CI 26.3, 38.6] ng/mL at 41 minutes after intramuscular injection.

Distribution
Plasma protein binding of ondansetron as measured in vitro was 70% to 76%, over the pharmacologic concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Elimination
Metabolism: Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.

Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron. The metabolites are observed in the urine.

In vitro metabolism studies have shown that ondansetron is a substrate for multiple human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 plays a predominant role while formation of the major in vivo metabolites is apparently mediated by CYP1A2. The role of CYP2D6 in ondansetron in vivo metabolism is relatively minor.

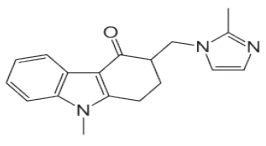
The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolizers of CYP2D6 and those who were extensive metabolizers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo.

Excretion: In adult cancer patients, the mean ondansetron elimination half-life was 4.0 hours, and there was no difference in the multidose pharmacokinetics over a 4-day period. In a dose-proportionality trial, systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values with an 8-mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

Nonclinical properties

Animal Toxicology or Pharmacology
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively (approximately 3.6 and 5.4 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, based on BSA). Ondansetron was not mutagenic in standard tests for mutagenicity.
Oral administration of ondansetron up to 15 mg/kg per day (approximately 3.8 times the recommended human intravenous dose, based on BSA) did not affect fertility or general reproductive performance of male and female rats.

Description
The active ingredient of ondansetron injection, USP is ondansetron hydrochloride, a selective blocking agent of the serotonin 5-HT3 receptor type. Its chemical name is (±) 1, 2, 3, 9-tetrahydro-9- methyl-3-[(2-methyl-1Himidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. The empirical formula is $C_{18}H_{19}N_3O{\bullet}HCl{\bullet}2H_2O$, representing a molecular weight of 365.9 g/mol.
It has the following structural:



Pharmaceutical particulars

Incompatibilities: Not applicable

Packaging Information: Ampoule of 2 ml

Storage: Store at temperature not exceeding 30°C, Protected from light.

Patient Counselling Information
Hypersensitivity Reactions
Inform patients that ondansetron injection may cause hypersensitivity reactions, some as severe as anaphylaxis and bronchospasm. The patient should report any signs and symptoms of hypersensitivity reactions, including fever, chills, rash, or breathing problems.

QT Prolongation
Patients should be informed that ondansetron injection may cause serious cardiac arrhythmias, such as QT prolongation. Patients should be instructed to tell their healthcare provider right away if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode.

Patients should be informed that the chances of developing severe cardiac arrhythmias, such as QT prolongation and Torsade de Pointes are higher in the following people:
- Patients with a personal or family history of abnormal heart rhythms, such as congenital long QT syndrome;
- Patients who take medications, such as diuretics, which may cause electrolyte abnormalities;
- Patients with hypokalemia or hypomagnesemia.

Ondansetron injection should be avoided in these patients, since they may be more at risk for cardiac arrhythmias, such as QT prolongation and Torsade de Pointes

Marketed by:
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