To be used by a Registered Medical Practitioners or a Hospital or a Laboratory

Ondansetron Injection I.P.
ONDEM INJECTION

1. NAME OF THE MEDICINAL PRODUCT
Ondansetron

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ONDEM 2ml injection contains:

Ondansetron Hydrochloride I.P.
equivalent to Ondansetron 2 mg
Water for injections I.P. q.s.

Each ONDEM 4ml injection contains:

Ondansetron Hydrochloride I.P.
equivalent to Ondansetron 4 mg
Water for injections I.P. q.s.

3. PHARMACEUTICAL FORM
Solution for injection
Clear and colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, Prevention and treatment of postoperative nausea and vomiting (PONV).

Paediatric Population:
Management of chemotherapy induced nausea and vomiting in children aged ≥6 months.
Prevention and treatment of postoperative nausea and vomiting in children aged ≥ 1 month.

4.2 Posology and Method of Administration
For intravenous injection or for 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.

Prevention of Postoperative Nausea and Vomiting:

- **Adult Use:** The recommended I.V. dosage of Ondansetron for adults is 4 mg undiluted administered intravenously is not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anaesthesia or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively 4mg undiluted may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of Ondansetron 4mg, administration of a second I.V. dose of 4 mg, Ondansetron postoperatively does not provide additional control of nausea and vomiting.
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- **Ampoule**: Ondansetron Injection
  REQUIRES NO DILUTION FOR ADMINISTRATION IN POST OPERATIVE NAUSEA AND VOMITING.

  Paediatric Use:
  The recommended I.V. Dosage of Ondansetron for paediatric patients is a single 0.1 mg/kg dose for paediatric patients weighing 40 kg or less, or a single 4-mg dose for paediatric patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anaesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery.

  Geriatric Use:
  The dosage recommendation is the same as for the general population.

  Prevention of Chemotherapy & Radiotherapy Induced Nausea and Vomiting:
  Adult Use:
  For patient receiving Emetogenic chemotherapy and radiotherapy, ondansetron can be given either by intravenous or intramuscular administration. For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8 mg should be administered as a slow intravenous or intramuscular injection or as a shorttime intravenous infusion over 15 immediately before treatment, followed by 8 mg orally twelve hourly.

  The recommended I.V. Dosage of Ondansetron is a single 32 mg dose or 0.15mg/kg/dose 8 hourly. The single 32 mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. With the three-dose (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. The recommended infusion rate should not exceed the 8 hourly (0.15 mg/kg) regimen. Subsequent doses (0.15 mg/kg) should be administered 4 and 8 hours after the first dose of Ondansetron. Ondansetron injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may be formed.
  Ampoule: Dilute Before Use.
  Ondansetron Injection should be diluted in 50 mL of 5% Dextrose

  Injection or 0.9% Sodium Chloride Injection before administration for prevention of chemotherapy induced nausea & vomiting.

  Paediatric Use:

The dosage in paediatric patients 6 months to 18 years of age,is 0.15 mg/kg/dose every 8 hours. The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy, subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of Ondansetron. Little information is available about dosage in paediatric cancer patients younger than 6 months of age.

Geriatric Use:
The dosage recommendation is same as for the general population.

Dose Modification
Safety and tolerability
Dosage Adjustment For Patients with Impaired Renal Function: The dosage recommendation is same as for the general population. There is no experience beyond first day administration of Ondansetron.

Dosage Adjustment For Patients With Impaired Hepatic Function : In patients with severe Hepatic impairement (Chid-pugh score of 10 or greater), a single maximal daily dose of 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first day administration of Ondansetron.

4.3 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.

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.

4.4 Special Warnings and Special Precautions for Use

Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

QT Prolongation
Ondansetron prolongs the QT interval in a dose-dependent manner. 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. 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 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 Palonosetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Palonosetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Palonosetron is used concomitantly with other serotonergic drugs.

Masking of Progressive Ileus and Gastric Distension
The use of Ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and gastric distention.

Effect on Peristalsis
Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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 studies 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 studies, leading to an increased cumulative dose in patient controlled administration (PCA) of tramadol.
Chemotherapy

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

Temazepam
The coadministration 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.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

4.7 Effects on Ability to Drive and Use Machines

Ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies. Till now no reported cases have been found.

4.8 Undesirable Effects

The following adverse reactions have been reported in clinical trials of adult patients treated with ondansetron, the active ingredient of intravenous Ondansetron across a range of dosages. A causal relationship to therapy with Ondansetron was unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting:

Adverse Reactions Reported in > 5% of Adult Patients who Received Ondansetron at a Dosage of Three 0.15-mg/kg doses were Diarrhea (16%), Headache (17%) and fever (8%).

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.

Postoperative Nausea and Vomiting:

The following adverse reactions been reported in ≥ 2% of adults receiving ondansetron at a dosage of 4 mg intravenous over 2 to 5 minutes in clinical trials.
Headache (17%), Drowsiness/sedation (8%), Injection site reaction (4%), Fever (2%), Cold sensation (2%), Pruritus (2%) and Paresthesia (2%).

Pediatric Use:
Rates of adverse reactions were similar in both the ondansetron and placebo groups in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered intravenously over at

least 30 seconds. Diarrhea was seen more frequently in patients taking Ondansetron (2%) compared to placebo (<1%) in the 1 month to 24 month age group. These patients were receiving multiple concomitant perioperative and postoperative medications.

Postmarketing Experience
The following adverse reactions have been identified during post-approval 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.

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, have also been reported.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Ondansetron is a potent, highly selective and competitive antagonist of the 5HT3 receptor, a subclass of serotonin receptors located on peripheral neurons and within the CNS. Chemotherapeutic agents and radiotherapy may cause release of 5HT (serotonin) from enterochromaffin cells in the visceral mucosa and initiate the emesis reflex and its accompanying feeling of nausea. Ondansetron selectively blocks the excitation of the presynaptic 5HT3 receptors of the peripheral neurons in this reflex and may exert additional actions within the CNS on 5HT3 receptors mediating the actions of vegal input to the area postrema. Ondansetron thus prevents nausea and vomiting. 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 have any extra-pyramidal side effects and does not alter plasma prolactin concentrations. Ondansetron Hydrochloride is (RS)-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-1, 2, 3, 9-tetrahydro-4H-carbazol-4-one hydrochloride dihydrate.

5.2 Pharmacokinetic Properties

An intravenous infusion of 8mg Ondansetron over 5 minutes gives peak plasma values of 80 to 100 mcg/l,which fall steadily over the subsequent 15 hours. A 4mg intravenous infusion of ondansetron given over 5minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection. The disposition of ondansetron following intramuscular and intravenous dosing in adults is similar with a terminal half-life of about 3 hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 months

6.2 Special Precautions for Storage

Store in a cool dry place protected from light

6.3 Nature and Contents of Container

Clear glass ampoules
2 ml: Pack sizes: Carton containing 15 ampoules.
4 ml: Pack sizes: Carton containing 15 ampoules.

7 Marketed By: Details

ALKEM

ALKEM LABORATORIES LTD.
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