ONDANSETRON SYRUP 2mg/5ml
ONDEM SYRUP

1. NAME OF THE MEDICINAL PRODUCT
Ondansetron

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains
Ondansetron hydrochloride IP
Equivalent to Ondansetron..... 2 mg
In a flavoured base..... q.s.

3. PHARMACEUTICAL FORM
Oral solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Adults
Ondansetron hydrochloride is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting.

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

4.2 Posology and Method of Administration

Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy
Adult use
The recommended adult oral dosage is one 8-mg ondansetron tablet or 20 ml (4 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron syrup given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ondansetron tablet or ondansetron MD tablet or 20 ml (4 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron syrup should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use
For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ondansetron tablet or ondansetron MD tablet or 10 ml

(2 teaspoonfuls equivalent to 4 mg of ondansetron) of ondansetron syrup given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ondansetron tablet or ondansetron MD tablet or 10 ml (2 teaspoonfuls equivalent to 4 mg of ondansetron) of ondansetron syrup should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Geriatric use
The dosage is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen

The recommended oral dosage is one 8-mg ondansetron tablet or ondansetron MD tablet or 20 ml (4 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron syrup given 3 times a day.
For total body irradiation, one 8-mg ondansetron tablet or ondansetron MD tablet or 20 ml (4 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron syrup should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.
For single high-dose fraction radiotherapy to the abdomen, one 8-mg ondansetron tablet or ondansetron MD tablet or 20 ml (4 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron syrup should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.
For daily fractionated radiotherapy to the abdomen, one 8-mg ondansetron tablet or ondansetron MD tablet or 20 ml (4 teaspoonfuls equivalent to 8 mg of ondansetron) of ondansetron syrup should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric use
There is no experience with the use of ondansetron tablets, MD tablet or ondansetron syrup in the prevention of radiation-induced nausea and vomiting in pediatric patients.

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

Postoperative Nausea and Vomiting
The recommended dosage is 16 mg given as two 8-mg ondansetron tablets or ondansetron MD tablet or 40 ml (8 teaspoonfuls equivalent to 16 mg of ondansetron) of ondansetron syrup 1 hour before induction of anesthesia.

Pediatric use
There is no experience with the use of ondansetron tablets, or ondansetron syrup in the prevention of postoperative nausea and vomiting in pediatric patients.

Geriatric use
The dosage is the same as for the general population
Dose Modification
Safety and tolerability
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 (5.4h). 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.

Elderly or renal impairment
Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

Hepatic impairment
Following oral, intravenous or intramuscular dosing 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. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

4.3 Contraindications
Hypersensitivity to any component of the preparation.

4.4 Special Warnings and Special Precautions for Use
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.
Very rarely and predominantly with intravenous Ondansetron, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.
As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.
In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

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

CINV: When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimes has not been investigated in clinical trials. Cross-trial comparison indicates similar efficacy for both regimes (section 5.1).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
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, morphine, lignocaine, thiopental and propofol.

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.
Tramadol: Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.
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 (see Warnings and Precautions).

4.6 Pregnancy and Lactation

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 foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

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.

4.7 Effects on Ability to Drive and Use Machines

None reported
In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8 Undesirable Effects

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). 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 from post-marketing spontaneous data.
The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

Table 1. Adverse Reactions Reported in Clinical Trials

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare (<1/10,000).
Immune system disorders				Immediate hypersensitivity reactions sometimes severe, including anaphylaxis	

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare (<1/10,000).
Nervous system disorders	Headache.		Seizures, movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae.	Dizziness during rapid IV administration.	
Eye disorders				Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.	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			Arrhythmias, chest pain with or without ST segment depression, bradycardia.		
Vascular disorders		Sensation of warmth or flushing.	Hypotension		

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare (<1/10,000).
Respiratory, thoracic and mediastinal disorders			Hiccups		
Gastrointestinal disorders		Constipation			
Hepatobiliary disorders			Asymptomatic increases in liver function tests#		

#These events were observed commonly in patients receiving chemotherapy with cisplatin.
Paediatric population
The adverse event profiles in children and adolescents were comparable to that seen in adults.

4.9 Overdose

Signs and Symptoms

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 Undesirable effects). 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.

Treatment

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established

5.2 Pharmacokinetic Properties

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass 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.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $t_{½}$ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended.

In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important.

5.3 Preclinical Safety Data

No additional data of relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life

24 months

6.2 Special Precautions for Storage

Store in cool place, protected from light

6.3 Nature and Contents of Container

30 ml in Amber PET bottle, in monocarton.

7. Manufactured & Marketed By:

ALKEM

ALKEM LABORATORIES LTD.
ALKEM HOUSE,
Senapati Bapat Marg,
Lower Parel,
Mumbai – 400 013.