SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Product Name: EMITINO TABLETS 8mg

(Ondansetron Orally Disintegrating Tablets USP 8mg)

2. Qualitative and quantitative composition:

Each Uncoated Tablets Contains

Ondansetron USP……. 8 mg

3. Pharmaceutical form: Tablets for Oral Use

4. Clinical particulars:

4.1 Therapeutic indications:

Emitino is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV), and for the prevention of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

4.2 Posology and method of administration

1) Prevention of Postoperative Nausea and Vomiting:

Adults:

The recommended I.V. dosage of Emitino for adults is 4 mg undiluted administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery.

Alternatively, 4 mg 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, pre-induction, I.V. dose of Ondansetron 4 mg, administration of a second I.V. dose of 4 mg Ondansetron postoperatively does not provide additional control of nausea and vomiting.

The recommended dosage is Ondansetron 16 mg given 1 hour before induction of anesthesia.

Children:

The recommended I.V. dosage of Emitino for pediatric surgical patients (1 month to 12 years of age) is a single 0.1-mg/kg dose for patients weighing 40 kg or less, or a single 4-mg dose for 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 anesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery.

There is no experience with the use of Emitino Tablets, in the prevention of postoperative nausea and vomiting in pediatric patients.

2) Prevention of Chemotherapy-Induced Nausea and Vomiting:

Adults:

Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer **Chemotherapy:**

The recommended I.V. dosage of Emitino for adults is a single 32-mg dose or three 0.15-mg/kg doses. A 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 prior to initiation of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of Emitino

The recommended adult oral dosage of Emitino is a single 24-mg tablet administered 30 minutes before the start of single-day highly emetogenic chemotherapy.

Children:

Prevention of Nausea and Vomiting Associated With highly or Moderately Emetogenic Cancer Chemotherapy:

The dosage in pediatric cancer patients 6 months to 18 years of age should be three 0.15-mg/kg doses. 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 Emitino.

The drug should be infused intravenously over 15 minutes. Little information is available about dosage in pediatric cancer patients younger than 6 months of age.

3) 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 Ondansetron 8-mg given 3 times a day.

For total body irradiation, Ondansetron 8-mg should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, Ondansetron 8-mg 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, Ondansetron 8-mg 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.

Children:

There is no experience with the use of Emitino Tablets, in the prevention of radiation-induced nausea and vomiting in pediatric patients.

4.3 Contraindications

Hypersensitivity to any components of the preparations

4.4 Special warnings and precautions for use

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of Ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention.

Ondansetron does not itself 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.

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.

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, lidocaine, thiopental or 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.

4.6 Pregnancy and lactation

Pregnancy

Category B. Emitino should be used during pregnancy only if clearly needed.

Lactation

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

Not known

4.8 Undesirable effects

Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. The following side effects can occur: headache, a sensation of flushing or warmth,

and occasional transient asymptomatic increases in aminotransferase and possible extrapyramidal reactions.

There have been rare reports of immediate hypersensitivity reactions including anaphylaxis. Rare cases of Oculogyric crisis, transient visual disturbances (e.g. blurred vision) and dizziness have been reported during rapid intravenous administration of Ondansetron.

4.9 Overdose

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

In addition to the adverse events 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 oral Ondansetron. 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 Particulars

5.1 Pharmacodynamic properties

ATC code:- A04 Antiemetics and antinauseants

ATC group:- A04AA0 1 Serotonin (5HT3) antagonist

Ondansetron is a potent, highly selective 5HTs 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 5HTs 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.

5.2 Pharmacokinetic properties

Following oral administration, Ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg 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). The disposition of Ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half-life of about three hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after IM and IV 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.

Special Patient Populations

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like Ondansetron.

In pediatric 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.

5.3 Preclinical safety data:

There are no pre-clinical data of relevance

6. Pharmaceutical particulars

6.1 List of excipients:

Excipients	Specification
Ammonium Glycyrrhizinate	BP
Sucralose	BP
Crospovidone	BP
Mannitol DC	BP
Avicel 200 (Microcrystalline Cellulose)	BP
Magnesium Stearate	BP
Colour Tartrazine Lake	IH
Aerosil 200 (Colloidal anhydrous Silica)	BP
Flavour Pineapple Powder DC106	IH

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protected from light..

6.5 Nature and contents of container

Primary Packing

10 Tablets are packed in Alu -Alu blister.

Secondary Packing:

10 blisters are packed in a Printed Carton with a pack insert

6.6 Special precautions for disposal and other handling

Not Applicable

7. 0 Name and Address of Manufacturer

Cachet Pharmaceuticals Pvt. Ltd

Village-Thana, Baddi, Dist-Solan,

Himachal Pradesh – 173 205

8.0 Marketing authorization holder

Cachet Pharmaceuticals Pvt. Ltd

415, Shah Nahar Industrial Estate,

Dr. E. Moses Road, Worli, Mumbai-400 018,

Maharashtra, India.

9. Marketing authorization number(s)

Not Applicable

10. Date of first authorization/renewal of the authorization

Not Applicable

11. Date of revision of the text

Not Applicable