SUMMARY OF PRODUCT CHARACTERISTICS

EMITINO TABLETS 4 mg

(Ondansetron Orally Disintegrating Tablets USP 4 mg)

1. Name of the medicinal product: EMITINO TABLETS 4 mg

(Ondansetron Orally Disintegrating Tablets USP 4 mg)

2. Qualitative and quantitative composition:

Each Uncoated tablet contains:

Ondansetron USP 4 mg

S. No.	Name of Material	Specification	Label Claim	Qty. mg/ tablet	Function
1	Ondansetron	USP	4.0 mg	4.124	Active Ingredient
2	Magna Sweet (Mono Ammonium Glycyrrhizinate)	USP	--	1.0	Sweetening Agent
3	Sucralose	BP	--	1.50	Sweetening agent
4	Crospovidone	BP	--	13.50	Disintegrating agent
5	Mannitol DC (Perlitol SD 160)	BP	--	34.78	Masking agent
6	Avicel 200 (Microcrystalline Cellulose 200)	BP	--	28.947	Diluent
7	Magnesium Stearate	BP	--	2.0	Lubricant
8	Colour Sunset yellow Lake	IH	--	0.75	Colouring Agent
9	Aerosil 200 (Colloidal anhydrous Silica)	BP	--	2.0	Glidant
10	Flavour Orange Powder (Trusil Bush Boake)	IH	--	0.70	Flavoring agent
11	Flavour Peppermint DC-117	IH	--	0.70	Flavouring agent
Total Weight				90.00	

3. Pharmaceutical form: Solid Dosage form (Tablets)

Light orange colour circular biconvex uncoated tablets having bisecting line on one side.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron is a potent, highly selective 5HT 3 receptor antagonist. It is 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 5HT 3 receptors. Ondansetron blocks the initiation of this reflex. Activation 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 nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT 3 receptors or 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.

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 anaesthesia, 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 anaesthesia.

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 Warnings and Precautions

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.

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4.6 Pregnancy

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 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. 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

Not known

4.8 Side effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <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.

Immune system disorders	
Rare:	Immediate hypersensitivity reactions, sometimes severe including anaphylaxis.
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 intravenous administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision), predominantly during 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	
Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Very rare:	Transient ECG changes including QT interval prolongation, predominantly with intravenous administration of ondansetron.
Vascular disorders	
Common:	Sensation of warmth or flushing.
Uncommon:	Hypotension.
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Hiccups.
Gastrointestinal disorders	
Common:	Constipation.
Hepatobiliary disorders	
Uncommon:	Asymptomatic increases in liver function tests. These events were observed commonly in patients receiving chemotherapy with cisplatin.
Pediatric population	
The adverse event profiles in children and adolescents were comparable to that seen in adults.	

4.9 Over dosage

Symptoms and Signs There is limited experience of ondansetron overdose. 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 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.

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5. Pharmacological properties

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 vomoting 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 normalized 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 paediatric 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.

6.0 Pharmaceutical particulars:

6.1 List of excipients:

Magna Sweet (Mono Ammonium Glycyrrhizinate), Sucralose, Crospovidone, Mannitol DC (Perlitol SD 160), Avicel 200 (Microcrystalline Cellulose 200), Magnesium Stearate, Colour Sunset yellow Lake, Aerosil 200(Colloidal anhydrous Silica), Flavour Orange Powder (Trusil Bush Boake), Flavour Peppermint DC-117.

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6.2 Incompatibilities:

Not Applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage:

Do no store above 30°C. Protect from light.

Keep out of reach of Children.

6.5 Nature and contents of container:

Alu-Alu Blister pack of 10 tablets.

6.6 Special precautions for disposal and other handling:

Not Applicable

7. Marketing Authorization Holder and Manufacturing site address:

Cachet Pharmaceuticals Pvt. Ltd

415, Shah Nahar Industrial Estate,

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

Maharashtra, India.

Manufacturer's Name and Address:

Cachet Pharmaceuticals PVT. LTD.

Village Thana, Baddi, Dist. Solan,

Himachal Pradesh – 173 205.

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8. Marketing authorisation number(s):

Rwanda FDA-HMP-MA-0067

9. Date of first authorisation/renewal of the authorization:

01 st June 2021

10. Date of revision of the text:

29.01.2024