	ATOZ Pharmaceuticals Pvt. Ltd. **Chennai – India.**
Product Name	**ONDERON MD (Ondansetron Orally Disintegrating Tablets USP 4mg)**
Composition	Each uncoated dispersible tablet contains: Ondansetron Hydrochloride Dihydrate USP Equivalent to Ondansetron 4mg
SUMMARY OF PRODUCT CHARACTERISTICS	

1. Name of the medicinal product

Ondansetron Orally Disintegrating Tablets USP 4mg

2. Qualitative and quantitative composition

Each uncoated dispersible tablet contains:

Ondansetron Hydrochloride Dihydrate USP Equivalent to Ondansetron 4mg

S. No.	Wt. / tablet (mg)	Ingredient	Spec.	Overages	Std. Qty for 200,000 tablets (in kg)
1.	4.96	Ondansetron Hydrochloride Dihydrate	USP	Nil	0.992
2.	105.19	Mannitol	BP	Nil	21.038
3.	6.25	Anhydrous Citric Acid	BP	Nil	1.250
4.	6.88	Sodium Bicarbonate	BP	Nil	1.376
5.	12.50	Crospovidone	BP	Nil	2.500
6.	2.50	Magnesium Stearate	BP	Nil	0.500
7.	0.15	Sucralose	BP	Nil	0.030
8.	1.25	Colloidal Anhydrous Silica	BP	Nil	0.250
9.	0.32	Trusil Orange Special Powder	IHS	Nil	0.064

*Represents solvents will not be present in the finished product.

USP-United States Pharmacopeaia, BP – British Pharmacopoeia & IHS-In House Specification.

3. Pharmaceutical form

Tablet: A white color circular shape biconvexed uncoated tablet, plain on both the sides.

4. Clinical particulars

4.1 Therapeutic indications

Ondansetron 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 (PONV).

4.2 Posology and method of administration

Oral use.

Chemotherapy and Radiotherapy induced nausea and vomiting:

Adults:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of ondansetron should be flexible in the range of 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy:

Ondansetron can be given either by rectal, oral (tablets or syrup), 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 immediately before treatment, followed by 8 mg orally twelve hourly.

For oral administration: 8 mg 1-2 hours before treatment, followed by 8 mg 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8 mg twice daily.

Highly emetogenic chemotherapy

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given by intravenous administration.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8 mg twice daily.

Children (aged 2 years and over) and adolescents (< 18 years)

Experience in paediatric patients is limited. In children older than two years, ondansetron may be administered as a single intravenous dose of 5 mg/m^2 over 15 minutes immediately before chemotherapy, followed by 4 mg orally twelve hours later. Oral treatment with a dose according to the body area should

be continued for up to 5 days after a course of treatment. Children with a total body area between 0.6 and 1.2 m^2 should receive a dosage schedule of 4 mg 3 times a day, while children with a body area above 1.2 m^2 should receive 8 mg 3 times a day.

There is no experience in children younger than 2 years old.

Ondansetron cannot be used in children with a total body surface below 0.6 m^2.

Elderly

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Please refer also to "Special populations".

Post-operative nausea and vomiting (PONV):

Adults

For the prevention of PONV ondansetron can be administered orally or by intravenous injection.

For oral administration:

16 mg one hour prior to anaesthesia.

Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg at eight hourly intervals.

Treatment of established PONV

For the treatment of established PONV intravenous administration is recommended.

Children (aged 2 years and over) and adolescents (< 18 years)

For the prevention and treatment of PONV slow intravenous injection is recommended.

Elderly

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting (PONV) in the elderly; however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Please refer also to"Special populations".

Special populations:

Patients with renal impairment

No alteration of daily dosage or frequency of dosing, or route of administration is required.

Patients with 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.

4.3 Contraindications

Hypersensitivity to ondansetron or to any of the excipients.

Hypersensitivity to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron).

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

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.

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is co-administered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Caution is advised if patients have received cardiotoxic agents and in patients with a history of prolonged QT syndrome.

This product contains 19.137 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ondansetron should not be used in children with a total body surface below 0.6 m^2.

The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.

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 medicinal products commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, propofol and thiopental.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolizing 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 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.

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 fetus, 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

Ondansetron has no or negligible influence on the ability to drive and use machines.

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 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000), not known (cannot be estimated from the available data)

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.

Very rarely transient ECG changes including QT interval prolongation have been reported

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.

There may be cross-sensitivity with other selective 5-HT_3- antagonists.

Nervous system disorders

Very common: Headache.

Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures.

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during rapid 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.

Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

Gastrointestinal disorders

Common:

Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests.

These events were observed commonly in patients receiving chemotherapy with cisplatin.

4.9 Overdose

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses.

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

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT_3) antagonists

Ondansetron is a potent, highly selective 5-HT_3 receptor-antagonist.

Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and

radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT3 receptors.

Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT3 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.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansetron does not alter plasma prolactin concentrations.

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

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (bioavailability is about 60%). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg 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 (5 hours) 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.)

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. 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 has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

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.

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.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical Particulars

6.1 List of excipients

Mannitol

Anhydrous Citric Acid

Sodium Bicarbonate

Crospovidone

Magnesium Stearate

Sucralose

Colloidal Anhydrous Silica

Trusil Orange Special Powder

6.2 Incompatibilities

None known.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's

1 x10's (10 tablets are packed in one Alu-Alu blister and 1 suchAlu-Alu blister is kept in one carton along with package insert).

6.6 Special precautions for disposal and other handling
Not applicable.
7. Marketing authorisation holder
Company name: INNOCIA LIFESCIENCES PVT. LTD., Address: Block A, No.12, Balaji Nagar, Ambattur, Chennai-600 053 Country: INDIA.
8. Marketing authorisation number(s)
Telephone: 044 26585811, 26585855 Telefax: - E-Mail: ah@innocialife.com