Summary of Product Characteristics

ONTIV® Tablet

ONTIV® Oral Solution

ONTIV®
(Ondansetron Hydrochloride)

1. NAME OF THE PRODUCT
ONTIV® (Ondansetron Hydrochloride) 8mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ONTIV® 8mg Tablet
Each film coated tablet contains:
Ondansetron Hydrochloride Dihydrate USP equivalent to Ondansetron.....8mg

3. PHARMACEUTICAL FORM
Tablet.

Appearance: Yellow colored, oblong shaped, film coated tablet, plain on both sides.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Adults:
ONTIV® is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
ONTIV® is indicated for the prevention of postoperative nausea and vomiting (PONV). For treatment of established PONV, administration by injection is recommended.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Adults:
Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV): The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used.
Emetogenic chemotherapy and radiotherapy: ONTIV® can be given orally. The recommended oral dose is 8mg taken 1-2 hours before chemotherapy or radiation treatment, followed by 8mg every 12 hours for a maximum of 5 days to protect against delayed or prolonged emesis. For highly emetogenic chemotherapy a single dose of up to 24mg ondansetron taken with 12mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used. To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron may be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8mg to be taken twice daily.

Dosing by BSA: Oral dosing can commence 12 hours later and may be continued for up to 5 days. The total dose over 24 hours (given as divided doses) must not exceed the adult dose of 32mg.
Dosing by body weight: Oral dosing can commence 12 hours later and may be continued for up to 5 days.
Elderly: No alteration of oral dose or frequency of administration is required.
Renal impairment: No alteration of daily dosage or frequency of dosing, or route of administration are 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 8mg should not be exceeded.
Patients with poor sparteine/debrisoquine metabolism: No alteration of daily dosage or frequency of dosing is required.
Post-operative nausea and vomiting (PONV): In adults for the prevention of PONV, the recommended oral dose is 16mg taken one hour prior to anaesthesia. In paediatric population, no studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting;
Elderly: There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly, however, ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

4.3. CONTRAINDICATIONS:

- Concomitant use with apomorphine is contraindicated.
- Hypersensitivity to the active substance.

4.4. SPECIAL WARNINGS:

- 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 attention. 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.
- Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmia's or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.
- Cases of myocardial ischemia have been reported in patients treated with ondansetron.

- Patients should be alerted to the signs and symptoms of myocardial ischaemia.
- Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.
- There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.
- 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.
- Patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

Lactose: Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

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.

Caution should be exercised when ondansetron is co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs).

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.
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.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Women of childbearing potential: Women of childbearing potential should consider the use of contraception.
Pregnancy: Ondansetron should not be used during the first trimester of pregnancy.
Breast-feeding: It is recommended that mothers receiving ondansetron should not breast-feed their babies.
Fertility: No information on the effects of ondansetron on human fertility.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:

Ondansetron has no or negligible influence on the ability to drive and use machines. In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8. UNDESIRABLE EFFECTS:

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).
Rare: Dizziness predominantly during rapid IV administration.
Eye disorders:
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare: Transient blindness predominantly during IV administration
Cardiac disorders:
Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare: QT prolongation (including Torsade de Pointes).
Not known: Myocardial ischemia.

Vascular disorders:
Common: Vascular disorders.
Uncommon: Hypotension.
Respiratory, thoracic and mediastinal disorders:
Uncommon: Hiccups.
Gastrointestinal disorders:
Common: Constipation.
Hepatobiliary disorders:
Uncommon: Asymptomatic increases in liver function tests.

4.9. OVERDOSE:

Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block. Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.
There is no specific antidote for ondansetron, therefore, in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Serotonin (5HT3) antagonist.
ATC code: A04AA01.
Mechanism of action: 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.

5.2. PHARMACOKINETIC PROPERTIES:

Absorption: 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. Mean bioavailability in healthy male following the oral administration of a single 8mg tablet, is approximately 55 to

60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.
Distribution: Ondansetron is not highly protein bound (70-76%).
Biotransformation and Elimination: 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.

5.3. PRECLINICAL SAFETY DATA:

Embryo-foetal development studies in rats and rabbits did not show evidence of harm to the foetus when ondansetron was administered during the period of organogenesis at approximately 6 and 24 times respectively the maximum recommended human oral dose of 24 mg/day, based on body surface area. In a pre- and postnatal developmental toxicity study, there were no effects upon pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance at approximately 6 times the maximum recommended human oral dose of 24 mg/day based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Microcrystalline cellulose
- Lactose anhydrous
- Pregelatinized starch
- Magnesium stearate
- Hydroxypropyl methyl cellulose
- Triacetin
- Titanium dioxide
- Yellow iron oxide color
- Purified water

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/Alu blister, pack size is 10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal product or waste material should be disposed off in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

114500

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

30th December, 2022

10. DATE OF REVISION OF THE TEXT

اونٹیو® ٹیبلٹ

(اونڈین سِٹرون ہائیڈروکلورائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

ONTIV®
(Ondansetron Hydrochloride)

1. NAME OF THE PRODUCT
ONTIV® (Ondansetron Hydrochloride) 4mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ONTIV® 4mg/5ml Oral Solution
Each 5ml contains:
Ondansetron Hydrochloride Dihydrate
eq. to Ondansetron.....4mg

3. PHARMACEUTICAL FORM
Oral solution

Appearance: Clear, colorless oral solution, having characteristic odor.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
ONTIV® is indicated for the prevention of nausea and vomiting associated with:

- highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50mg/m^2
- initial and repeat courses of moderately emetogenic cancer chemotherapy
- radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen

ONTIV® is also indicated for the prevention of postoperative nausea and/or vomiting.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Chemotherapy and radiotherapy induced nausea and vomiting (CINV)
Adults: The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.
Emetogenic chemotherapy and radiotherapy: Ondansetron can be given by rectal, oral (tablets or oral solution) intravenous or intramuscular administration.
For oral administration: 8mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8mg every 12 hours for a maximum of 5 days to protect against delayed or prolonged emesis.

For highly emetogenic chemotherapy: a single dose of up to 24mg ondansetron taken with 12mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used. 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 8mg twice daily.

Paediatric Population: CINV in children aged ≥ 6 months and adolescents. The dose for CINV can be calculated based on body surface area (BSA) or weight, see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing. There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA: Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5mg/m^2. The intravenous dose must not exceed 8mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days. The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥ 6 months and adolescents.

BSA	Day 1	Days 2 – 6 *
< 0.6m^2	2mg after 12 hrs	2mg every 12 hours
≥ 0.6m^2 to ≤ 1.2 m^2	4mg after 12 hrs	4mg every 12 hrs
>1.2m^2	8mg after 12 hours	8mg every 12 hours

* The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Dosing by bodyweight: Weight-based dosing results in higher total daily doses compared to BSA-based dosing. Oral dosing can commence twelve hours later and may be continued for up to 5 days. The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Table 2: Weight-based dosing for Chemotherapy - Children aged ≥ 6 months and adolescents.

Weight	Day 1	Days 2 – 6 *
≤ 10kg	Up to 3 doses of 0.15 mg/kg every 4 hours	2mg every 12 hours
>10kg	Up to 3 doses of 0.15 mg/kg every 4 hours	4mg every 12 hrs

* The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Elderly: Ondansetron is well tolerated by patients over 65 years. No alteration of oral dose or frequency of administration is required.

Post operative nausea and vomiting (PONV):

Adults: For the prevention of PONV: Ondansetron can be administered orally. For oral administration: 16mg one hour prior to anaesthesia.

Paediatric population: PONV in children aged ≥ 1 month and adolescents.

Oral formulation: No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting.

Elderly: There is limited experience in the use of Ondansetron in the prevention and treatment of PONV in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy. For both indications.

Patients with Renal impairment: No alteration of daily dosage or frequency of dosing, or route of administration are 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 8mg should not be exceeded.

Patients with poor Sparteine/Debrisoguine Metabolism: The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

Method of administration:

For oral use only.

4.3. CONTRAINDICATIONS:

ONTIV® oral solution is contraindicated in patients:

- known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any of the components of the formulation.
- receiving concomitant apomorphine due to the risk of profound hypotension and loss of consciousness.

4.4. SPECIAL WARNINGS AND 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. If hypersensitivity reactions occur, discontinue use of Ondansetron; treat promptly per standard of care and monitor until signs and symptoms resolve.

QT Prolongation: Electrocardiogram (ECG) changes, including QT interval prolongation have been seen in patients receiving ondansetron. In addition, postmarketing cases of Torsade de Pointes have been reported in patients

using Ondansetron oral solution. Avoid Ondansetron oral solution 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 alone. 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 oral solution 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, diarrhoea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Ondansetron oral solution and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Ondansetron oral solution and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Ondansetron oral solution is used concomitantly with other serotonergic drugs.

Myocardial Ischemia: Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms appeared immediately after administration but resolved with prompt treatment. Coronary artery spasm appears to be the most common underlying cause. Therefore, monitor or advise patients for signs or symptoms of myocardial ischemia after oral administration of Ondansetron.

Masking of Progressive Ileus and Gastric Distension: The use of Ondansetron oral solution in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction.

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

Ondansetron oral solution contains sodium benzoate which may increase jaundice (yellowing of the skin and eyes) in new born babies.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

Serotonergic Drugs: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including SSRIs and SNRIs. Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue Ondansetron oral solution and initiate supportive treatment.

Drugs Affecting Cytochrome P-450 Enzymes: 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 P450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. 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 oral solution is recommended for patients on these drugs.

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small trials indicate that when used together, Ondansetron oral solution may increase patient-controlled administration of tramadol. Monitor patients to ensure adequate pain control when ondansetron is administered with tramadol.

Chemotherapy: Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

Alfentanil and Atracurium: Ondansetron oral solution does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anaesthetics have not been studied.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Women of childbearing potential should consider the use of contraception. No information on the effects of ondansetron on human fertility. The available epidemiological studies on cardiac malformations show conflicting results. Animal studies does not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Pregnancy: Ondansetron should not be used during the first trimester of pregnancy. Based on human data from epidemiological studies, ondansetron is suspected to increase the risk of orofacial malformations, particularly oral clefts, when administered during the first trimester of pregnancy.

Breast-feeding: It is recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:

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

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

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 <1/100), 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.

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

Rare: Dizziness during rapid IV administration

Eye disorders:

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

Very rare: Transient blindness predominantly during intravenous administration

Cardiac disorders:

Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia

Rare: QTc prolongation (including Torsades de Pointes)

Unknown: Myocardial ischemia

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.

Skin: Urticaria, Stevens-Johnson syndrome and toxic epidermal necrolysis.

4.9. OVERDOSE:

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy.

In addition to the adverse reactions listed above, the following adverse reactions 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 72mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48mg of Ondansetron oral solution tablets. Following infusion of 32mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the adverse reactions resolved completely.

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg per kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachynoea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Serotonin (5HT3) antagonist

ATC code: A04AA01

Mechanism of action: Ondansetron is a selective 5-HT3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron’s antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT3 receptors and initiate the vomiting reflex.

5.2. PHARMACOKINETIC PROPERTIES:

Absorption: Ondansetron is absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8mg tablet, is approximately 56%. Ondansetron systemic exposure does not increase proportionately to dose. The area under curve (AUC) from a 16-mg tablet was 24% greater than predicted

from an 8-mg tablet dose. This may reflect some reduction of firstpass metabolism at higher oral doses.
Food Effects: Bioavailability is also slightly enhanced by the presence of food.
Distribution: Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10 to 500ng/mL. Circulating drug also distributes into erythrocytes.
Biotransformation: Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways.
Elimination: Metabolism and Excretion: Ondansetron is extensively metabolized in humans, with approximately 5% of a radio-labeled dose recovered as the parent compound from the urine. The metabolites are observed in the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.

5.3. PRECLINICAL SAFETY DATA:

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10mg/kg per day and 30mg/kg per day, respectively (approximately 4 and 6 times the maximum recommended human oral dose of 24mg per day, based on BSA). Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15mg/kg per day (approximately 6 times the maximum recommended human oral dose of 24mg per day, based on BSA) did not affect fertility or general reproductive performance of male and female rats.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Sorbitol Solution
- Sodium Benzoate
- Citric Acid Anhydrous
- Sodium Citrate
- Peppermint Flavor
- Peach Flavor
- Purified Water

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C and protect from heat, light and freezing.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Amber glass bottle with tamper-proof aluminium cap with P.E. wad, pack size is 50ml.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Tightly close the cap after use. Medicine should not be used if container is leaking or it contains undissolved particles(s). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
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اونٹیو® اورل سلوشن

(اونڈین سِٹرون
ہائیڈروکلورائیڈ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور منجمد ہونے سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

دوا کے لیک ہونے یا اس میں کوئی غیر حل پزیر شے

نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔