SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

ONTIV™ **(Ondansetron Hydrochloride) 4mg/2ml Injection**

ONTIV™ **(Ondansetron Hydrochloride) 8mg/4ml Injection**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ONTIV™ **4mg/2ml Injection**	**ONTIV**™ **8mg/4ml Injection**
Each 2ml contains:	Each 4ml contains:
Ondansetron Hydrochloride Dihydrate USP eq. to Ondansetron.....4mg	Ondansetron Hydrochloride Dihydrate USP eq. to Ondansetron.....8mg

3. PHARMACEUTICAL FORM

Solution for injection.

Appearance:

ONTIV™ **4mg/2ml Injection:** Clear, colourless solution, free from foreign particles.

ONTIV™ **8mg/4ml Injection:** Clear, colourless solution, free from foreign particles.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Adults: 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).

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

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Ondansetron 4mg/2ml Injection / Ondansetron 8mg/4ml Injection: For intravenous injection or after dilution for intravenous infusion.

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 8-32mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy: For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by oral or intravenous administration.For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8mg should be administered as a slow intravenous injection (in not less than 30 seconds) or as a short-time intravenous infusion over 15 minutes immediately before treatment, followed by 8mg orally twelve hourly. 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. ***Highly emetogenic chemotherapy:*** For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given either by oral, rectal, or intravenous administration. Ondansetron is equally effective in the following dose schedules over the first 24 hours of chemotherapy:

● A single dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy. ● A dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injections (in not less than 30 seconds) or intramuscular doses of 8mg four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours. ● A maximum initial intravenous dose of 16mg diluted in 50-100ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of Ondansetron may be followed by two additional 8mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.

A single dose greater than 16mg must not be given due to dose-dependent increase of QT prolongation risk. The selection of dose regimen should be determined by the severity of the emetogenic challenge. The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy. 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.

Paediatric population: Chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months to 17 years: The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50ml of saline or other compatible infusion fluid and infused over not less than 15 minutes. Weight-based dosing results in higher total daily doses compared to BSA-based dosing. Ondansetron injection should be diluted in 5% dextrose or 0.9% Sodium Chloride or other compatible infusion fluid and infused intravenously over not less than 15 minutes. There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged CINV. There is 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 single intravenous dose must not exceed 8mg. 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 adult dose of 32mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥ 6 months to 17 years:

BSA	Day 1 [a,b]	Day 2-6 [b]
< 0.6m^2	5mg/m^2 IV plus 2mg syrup after 12 hours	2mg syrup every 12 hours
> 0.6m^2 to ≤ 1.2m^2	5mg/m^2 IV plus 4mg syrup or tablet after 12 hours	4mg syrup or tablet every 12 hours
≤ 1.2m^2	5mg/m^2 or 8mg IV Plus 8mg syrup or tablet after 12 hours	8mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8mg.
b 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.Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15mg/Kg. The single intravenous dose must not exceed 8mg.On day 1, two further intravenous doses may be given in 4-hourly intervals.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 adult dose of 32mg.

Table 2: Weight-based dosing for Chemotherapy - Children aged ≥ 6 months to 17 years:

Weight	Day 1 [a,b]	Day 2-6 [a,b]
≤ 10 kg	Up to 3 doses of 0.15mg/kg IV every 4 hours	2mg syrup every 12 hours
> 10 kg	Up to 3 doses of 0.15mg/kg IV every 4 hours	4mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8mg.
b The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Elderly: In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid and infused over 15 minutes. In patients 75 years of age or older, the initial intravenous dose of ondansetron should not exceed 8mg. All intravenous doses should be diluted in 50-100ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid and infused over 15 minutes. The initial dose of 8mg may be followed by two further intravenous doses of 8mg, infused over 15 minutes and given no less than four hours apart.

Post-Operative Nausea and Vomiting (PONV): Adults: ***Prevention of PONV For the prevention of PONV:*** Ondansetron can be administered orally or by intravenous injection. Ondansetron may be administered as a single dose of 4mg given by slow intravenous or intramuscular injection at induction of an anaesthesia. ***Treatment of established PONV: For treatment of established PONV:*** A single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population: ***PONV in children aged ≥ 1 month to 17 years:*** For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia. For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg. There is no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

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.

Special Populations:***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 intravenously should not be exceeded and therefore parenteral or oral administration is recommended. ***Patients with poor sparteine/Debrisoquine metabolism:***The elimination half-life of ondansetron is not altered in subjects classified as poor metabolizers 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 is require.

4.3. CONTRAINDICATIONS:
Hypersensitivity to ondansetron or to other selective 5-HT_3 -receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients. Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions. Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, conduction disturbances, and in patients taking anti-arrhythmic agents or beta-adrenergic blocking agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration. Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischemia. There have been post-marketing reports describing patients with potentially life-threatening serotonin syndrome (including altered mental status, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs), and opioid/opiate medicines (e.g. buprenorphine)). 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 sub-acute 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 a mg/kg basis and administering three doses at 4-hour intervals, the total daily dose will be higher than if one single dose of 5mg/m^2 followed by an oral dose is given. This medicine contains less than 1mmol sodium (23mg) per ml of injection, that is to say essentially "sodium free". However, if a solution of common salt (0.90% w/v sodium chloride solution) is used for the dilution of ondansetron prior to administration then the dose of sodium received would be higher.

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. There are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental, or propofol. Ondansetron is metabolized 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. Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval (including some cytotoxics) and/or cause electrolyte abnormalities. The 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.
Serotonergic Drugs (e.g. SSRIs and SNRIs): 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). There are also reports of serotonin syndrome when ondansetron is used concomitantly with opioid/opiate medicines, e.g. buprenorphine.
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: Ondansetron may reduce the analgesic effect of tramadol.

4.6. FERTILITY, PREGNANCY AND LACTATION:
Fertility: There are no effects of ondansetron on human fertility.
Pregnancy: Women of childbearing potential should consider the use of contraception. Ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy. Ondansetron should not be used during the first trimester of pregnancy. ***Pregnancy testing:*** Pregnancy status should be verified in women of child-bearing potential before starting the treatment with ondansetron.
Breastfeeding: Recommended that mothers receiving ondansetron should not breastfeed 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. 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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and unknown (cannot be estimated from the available data). Very common, common, and uncommon events. 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). ***Rare:*** Dizziness predominantly during rapid IV administration.
Eye Disorders: ***Rare:*** Transient visual disturbances (e.g. blurred vision) predominantly during rapid 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 Torsade 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 and subcutaneous tissue disorders: ***Very rare:*** Toxic skin eruption, including toxic epidermal necrolysis.
General disorders and administration site conditions: ***Common:*** Local IV injection site reactions.
Paediatric population: The adverse event profiles in children and adolescents were comparable to that seen in adults.

4.9. OVERDOSE:
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. Ondansetron prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.
Paediatric population: 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. **ATC Code:** A04AA01.
Mechanism of Action: Ondansetron is a potent, highly selective 5-HT_3 receptor antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause the release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT_3 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 nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5-HT_3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in postoperative 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:
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. Mean bioavailability, 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. A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection. 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.

5.3. PRECLINICAL SAFETY DATA:
Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma ratio was 5.2. Ondansetron in submicromolar concentrations blocked cloned HERG Potassium channels of the human heart. The clinical relevance of this finding is not clear.

SUMMARY OF PRODUCT CHARACTERISTICS

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

ONTIV™ 4mg/2ml Injection: ● Sodium chloride ● Citric acid monohydrate ● Sodium citrate dihydrate ● Water for Injection

ONTIV™ 8mg/4ml Injection: ● Sodium chloride ● Citric acid monohydrate ● Sodium citrate dihydrate ● Water for Injection

6.2. INCOMPATIBILITIES:

Ondansetron injection should only be mixed with recommended solutions that are 0.9% of Sodium Chloride, 5% Glucose, 10% Manitol, Ringer's solution, 0.3% Potassium Chloride and 0.9% Sodium Chloride solution and 0.3% Potassium Chloride and 5% Glucose solution for infusion. Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

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.

6.5. NATURE AND CONTENTS OF CONTAINER:

ONTIV™ 4mg/2ml Injection: 5ml clear ampoule USP Type-I, pack size of 1 x 4ml ampoule.

ONTIV™ 8mg/4ml Injection: 3ml clear ampoule USP Type-I, pack size of 1 x 2ml ampoule.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

For single use only. Any unused solution should be discarded. The solution should be visually inspected prior to use. Only clear and colourless solutions practically free from particles should be used.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Ondansetron may be administered by intravenous infusion by 1mg/hour. The following medicinal products may be administered only via a Y-site of an infusion set in concentrations of ondansetron of 16 to 160 micrograms/ml (e.g. 8mg/500ml and 8mg/50ml respectively): Dexamethasone-21-dihydrogenphosphate disodium, Cisplatin, Carboplatin, Fluorouracil, Etoposide, Ceftazidime, Cyclophosphamide, Doxorubicin.

6.7. DRUG PRODUCT SPECIFICATIONS:

USP Specs.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

ONTIV™ 4mg/2ml Injection: 116249

ONTIV™ 8mg/4ml Injection: 116250

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8th August 2023

10. DATE OF REVISION OF THE TEXT

Date the day of approval:

INSTRUCTIONS

Dosage: As directed by the physician.
To be sold on prescription of a registered medical practitioner only.
Keep out of the reach of children.
Injection should not be used if container is leaking, solution is cloudy or it contains undissolved particle(s).

اونٹیو™ انجکشن

(اونڈینسٹرون ہائیڈروکلورائیڈ)

ہدایات:

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال 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۔

انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔