Appendix No. 5

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

ONDANSETRON ORALLY DISINTEGRATING TABLETS USP 4 MG

2. Qualitative and quantitative composition

ACTIVE INGREDIENTS				
APPROVED NAME	**SPECIFICATION OR REFERENCE TEXT**	**QTY/ TABLET**		**% OVERAGES**
		MG/TABLET	**%W/W/TABLET**	
Ondansetron hydrochloride* Eq.to Ondansetron	USP	5.200 mg 4.000 mg	1.824 %	30.00 %

INACTIVE INGREDIENTS				
APPROVED NAME	**SPECIFICATION OR REFERENCE TEXT**	**QTY/ TABLET**		**REASON FOR INCLUSION**
		MG/TABLET	**%W/W/TABLET**	
Microcrystalline cellulose	BP	210.80 mg	73.974 %	Diluent
Croscarmellose sodium	BP	10.00 mg	3.508 %	Disintegrant
Polacrilin potassium	USP	12.000 mg	4.210 %	Disintegrant
Sodium bicarbonate	BP	9.000 mg	3.157 %	Buffering agent
Sunset yellow colour	INHOUSE	4.000 mg	1.403 %	Colour
Magnesium stearate	BP	4.000 mg	1.403 %	Lubricant
Colloidal silicone dioxide	USP	4.000 mg	1.403 %	Glidant
Purified talc	BP	4.000 mg	1.403 %	Glidant
Sucralose	BP	10.000 mg	3.508 %	sweetner
Essence orange dry	INHOUSE	12.000 mg	4.210 %	Flavour

*30.00 % Overages are added on label claim

3. Pharmaceutical form

Oral tablet

4. Clinical particulars

4.1 Therapeutic indications

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m^2.
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
- Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, Ondansetron Orally Disintegrating Tablets, are recommended even where the incidence of postoperative nausea and/or vomiting is low.

4.2 Posology and method of administration

Do not attempt to push ondansetron orally disintegrating tablets through the foil backing. With dry hands, peel back the foil backing of 1 blister and gently remove the tablet. Immediately place the ondansetron orally disintegrating tablets on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.
For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg Ondansetron orally disintegrating tablets given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg Ondansetron orally disintegrating tablets should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

4.3 Contraindications

The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.
Ondansetron orally disintegrating tablets are contraindicated for patients known to have hypersensitivity to the drug.

4.4 Special warnings and precautions for use

- Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HTs receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.
- Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. 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. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, or patients taking other medicinal products that lead to QT prolongation. Therefore, caution should be exercised in patients with cardiac rhythm or conduction

disturbances, in patients treated with antiarrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

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

Paediatric Population

Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

CINV

When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicates similar efficacy for both regimens.

4.5 Interaction with other medicinal products and other forms of interaction

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 available data, no dosage adjustment is recommended for patients on these drugs.

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

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), 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 is recommended for patients on these drugs.

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.

Chemotherapy: Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

Use in Surgical Patients:The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

4.6 Pregnancy and lactation

Pregnancy-Teratogenic Effects***:***

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman. Pediatric Use: Little information is available about dosage in pediatric patients 4 years of age or younger.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8 Undesirable effects

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of Ondansetron tablets. A causal relationship to therapy with Ondansetron tablets has been unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting
The adverse events in Table have been reported in ≥ 5% of adult patients receiving a single 24-mg Ondansetron Tablet in trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥ 50 mg/m^2).

Single Day Therapy With 24-mg Ondansetron tablets (Highly Emetogenic Chemotherapy)

Event	**Ondansetron 24 mg q.d. n = 300**	**Ondansetron 8 mg b.i.d. n=124**	**Ondansetron 32 mg q.d. n=117**
Headache	33(11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table have been reported in ≥ 5% of adults receiving either 8 mg of Ondansetron tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

3 Days of Therapy With 8-mg Ondansetron tablets (Moderately Emctogcnic Chemotherapy)

Event	**Ondansetron 8 mg b.i.d. n = 242**	**Ondansetron 8 mg t.i.d. n = 415**	**Placebo n = 262**
Headache	58 (24%)	113(27%)	34(13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)

Constipation	22 (9%)	26 (6%)	1 (< 1%)
Diarrhea	15 (6%)	16(4%)	10 (4%)
Dizziness	13 (5%)	18(4%)	12 (5%)

Central Nervous System: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.
Hepatic: In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving Ondansetron tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.
There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.
Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.
Other: Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to Ondansetron tablets was unclear.
Radiation-Induced Nausea and Vomiting
The adverse events reported in patients receiving Ondansetron tablets and concurrent radiotherapy were similar to those reported in patients receiving Ondansetron tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.
Postoperative Nausea and Vomiting
The adverse events in Table 7 have been reported in > 5% of patients receiving Ondansetron tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Frequency of Adverse Events From Controlled Studies With Ondansetron tablets (Postoperative Nausea and Vomiting)

Adverse Event	**Ondansetron 16 mg (n = 550)**	**Placebo (n = 531)**
Wound problem	152 (28%)	162(31%)
Drowsiness/sedation	112(20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18(3%)

Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when Ondansetron Orally Disintegrating Tablets are taken with water, when compared to without water.
Observed During Clinical Practice:
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of Ondansetron tablets. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to Ondansetron tablets.
Cardiovascular: Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.
General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.
Hepatobiliary: Liver enzyme abnormalities
Lower Respiratory: Hiccups
Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions
Skin: Urticaria
Special Senses: Eye Disorders: Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.
Drug Abuse And Dependence:
Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

4.9 Overdose

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of Ondansetron Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 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 enterochromaffm cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.
In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.
In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.
Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

5.2 Pharmacokinetic properties

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg tablet, is approximately 56%.
Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses. Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids.
Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of Ondansetron.
In vitro metabolism studies have shown that Ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall Ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing Ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of Ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3 A4 inducers, carbamazepine, or phenytoin, reduction in AUC, Cmax, and T½ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended.
In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics 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 explaine by differences in

body weight between men and women. It is not known whether these gender-related differences were clinically important.

5.3 Preclinical safety data

No additional data of relevance.

6. Pharmaceutical particulars

6.1 List of Excipients

- Microcrystalline cellulose
- Croscarmellose sodium
- Polacrilin potassium
- Sodium bicarbonate
- Sunset yellow colour
- Magnesium stearate
- Colloidal silicone dioxide
- Purified talc
- Sucralose
- Essence orange dry

6.2 Incompatibilities

None reported.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and contents of container

3 x 10 Tablets Alu-Alu Pack, Printed and Laminated Carton

6.6 Special precautions for disposal and other handling

Not Applicable.

7. Marketing authorization holder

West-Coast Pharmaceutical Works Ltd, Ahmedabad.

8. Marketing authorization number(s)

Not applicable.

9. Date of first authorization/renewal of the authorization

Not applicable.

10. Date of revision of the text

June, 2017

Appendix No. 6

PATIENT INFORMATION LEAFLET

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NOT APPLICABLE