

**Summary Product Characteristics (SPC):**

Enclosed

**1. Name of the medicinal product: EMESAFE-4 (ONDANSETRON ORALLY DISINTEGRATING TABLETS USP 4 MG)**

**2. Qualitative and Quantitative composition:**

Sr. No	Ingredients	Specification	Label Claim (mg)	Qty/tab (mg)	Overages	Reason for inclusion
<b>ACTIVE</b>						
1.	Ondansetron Hydrochloride	USP	4.00	4.99	--	Active
<b>EXCIPIENT</b>						
2.	Magna Sweet	IHS	--	2.00	--	Sweetner
3.	Aspartame	BP	--	8.00	--	Sweetner
4.	Croscarmellose Sodium	BP	--	12.00	--	Disintegrant
5.	Crospovidone	BP	--	6.00	--	Binder
6.	Indion resins 234	IHS	--	5.00	--	Taste masking Agent
7.	Microcrystalline Cellulose 102	BP	--	41.51	--	Diluent
8.	Magnesium Stearate	BP	--	2.00	--	Lubricant
9.	Colloidal Silicon Dioxide	BP	--	2.00	--	Glidant
10.	Flavour Strawberry	IHS	--	0.50	--	Flavouring Agent
<b>Weight of Tablet</b>				84 mg/tab	--	--

Where, USP: United States Pharmacopoeia, BP: British Pharmacopoeia, IHS: In-House Specification, q.s.: quantity sufficient

- Molecular weight of Ondansetron Hydrochloride is 365.86 mg equivalent to Molecular weight of Ondansetron 293.36
- Therefore, 4.99 mg of Ondansetron Hydrochloride is equivalent to Molecular weight of Ondansetron 4.00 mg

### 3. Pharmaceutical Form: Uncoated Tablet

### 4. Clinical Particulars:

#### 4.1 Therapeutic Indications

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin  $\geq 50 \text{ mg/m}^2$ .
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
3. 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.
4. 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

**Instructions for Use/Handling Ondansetron Orally Disintegrating Tablets:** 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.

**Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy:** The recommended adult oral dosage of Ondansetron Tablet is 24 mg given as three 8-mg tablets administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin  $\geq 50 \text{ mg/m}^2$ . Multiday, single-dose administration of a 24 mg dosage has not been studied.

**Pediatric Use:** There is no experience with the use of a 24 mg dosage in pediatric patients.

**Geriatric Use:** The dosage recommendation is the same as for the general population.

**Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy:** The recommended adult oral dosage is one 8-mg Ondansetron Orally Disintegrating Tablets given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg Ondansetron Orally Disintegrating Tablets should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

**Pediatric Use:** 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.

**Geriatric Use:** The dosage is the same as for the general population.

**Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen:** The recommended oral dosage is one 8-mg Ondansetron Orally Disintegrating Tablets given 3 times a day. For total body irradiation, one 8-mg Ondansetron Orally Disintegrating Tablets should be administered 1 to 2 hours before each fraction of radiotherapy administered each day. For single high-dose fraction radiotherapy to the abdomen, one 8-mg Ondansetron Orally Disintegrating Tablets or should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen, one 8-mg Ondansetron Orally Disintegrating Tablets should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

**Pediatric Use:** There is no experience with the use of Ondansetron Orally Disintegrating Tablets in the prevention of radiation-induced nausea and vomiting in pediatric patients.

**Geriatric Use:** The dosage recommendation is the same as for the general population.

**Postoperative Nausea and Vomiting:** The recommended dosage is 16 mg given as two 8-mg Ondansetron Orally Disintegrating Tablets 1 hour before induction of anesthesia.

**Pediatric Use:** There is no experience with the use of Ondansetron Orally Disintegrating Tablets in the prevention of postoperative nausea and vomiting in pediatric patients.

**Geriatric Use:** The dosage is the same as for the general population.

**Dosage Adjustment for Patients With Impaired Renal Function:** The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

**Dosage Adjustment for Patients With Impaired Hepatic Function:** In patients with severe hepatic impairment (Child-Pugh<sup>2</sup> score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

#### **4.3 Contraindications**

Concomitant use with apomorphine. Hypersensitivity to any component of the preparation.

#### **4.4 Special warnings and precautions for use**

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT<sub>3</sub>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. 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, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

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 with rare hereditary problems of galactose intolerance, 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-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m<sup>2</sup> 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**

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental, or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Caution should be exercised when ondansetron is coadministered 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.

**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).

**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 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 foetus, 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.

### Breast-feeding

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron Orally Disintegrating Tablets should not breast-feed their babies.

### Fertility

There is no information on the effects of ondansetron on human fertility.

## **4.7 Effects 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ) and very rare ( $< 1/10,000$ ). Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron. The adverse event profiles in children and adolescents were comparable to that seen in adults.

### **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) <sup>(1)</sup>.

Rare: Dizziness predominantly during rapid IV administration.

### **Eye disorders**

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

Very rare: Transient blindness predominantly during IV administration <sup>(2)</sup>.

### **Cardiac disorders**

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

Rare: QTc prolongation (including Torsade de Pointes).

### **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 <sup>(3)</sup>.

1. Observed without definitive evidence of persistent clinical sequelae.
2. 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.
3. These events were observed commonly in patients receiving chemotherapy with cisplatin.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

## **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 fashion. ECG monitoring is recommended in cases of overdose.

### Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

### Treatment

There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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 Particulars:**

### **5.1 Pharmacodynamic properties**

**Pharmacotherapeutic Group :** Antiemetics and antinauseants, Serotonin (5-HT<sub>3</sub>) antagonists  
**ATC No.:** A04AA01

### Mechanism of Action

Ondansetron is a potent, highly selective 5HT<sub>3</sub> 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 5HT<sub>3</sub> 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 5HT<sub>3</sub> 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.

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

### QT Prolongation

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women.

Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec.

### Paediatric population:

#### CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m<sup>2</sup> intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m<sup>2</sup> intravenous and ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous and placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m<sup>2</sup> intravenous together with 2 to 4 mg dexamethasone orally
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. of children n = 28). Complete control of emesis was achieved in 42% of patients.

#### PONV

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 3 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p <0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3: Prevention and treatment of PONV in Paediatric Patients – Treatment response over 24 hours

Study	Endpoint	Ondansetron %	Placebo %	p value
S3A380	CR	68	39	≤0.001
S3GT09	CR	61	35	≤0.001
S3A381	CR	53	17	≤0.001
S3GT11	no nausea	64	51	0.004
S3GT11	no emesis	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

#### **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 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. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

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.

A 4mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/mL. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/mL are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/mL are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

#### Special Patient Populations:

##### Gender

Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

##### Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

#### Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects ( $\geq 65$  years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients  $\geq 75$  years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing.

#### Renal impairment

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 (5.4 hours). 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.

#### Hepatic impairment

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 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

### **5.3 Pre-clinical Safety:**

No additional data of relevance.

## **6. Pharmaceutical Particulars:**

### **6.1 List of Excipients:**

Magna Sweet	IHS
Aspartame	BP
Croscarmellose	
Sodium	BP
Crospovidone	BP
Indion resins 234	IHS
Microcrystalline Cellulose 102	BP
Magnesium Stearate	BP
Colloidal Silicon	
Dioxide	BP
Flavour Strawberry	IHS

### **6.2 Incompatibilities:** Nil.

### **6.3 Shelf Life:**

36 months.

### **6.4 Special Precautions for storage:**

Store below 30°C in a dry place. Protect from light.

### **6.5 Nature and contents of container:**

10 Alu-Alu blisters of 10 tablets each, packed in a primary carton along with pack insert.

### **6.6 Special precautions for disposal and other handling:**

No special requirements.

## **7. Marketing Authorization Holder:** VAPI CARE PHARMA PVT. LTD.

## **8. Marketing Authorization Number:** --

## **9. Date of first Authorization /renewal of the authorization:** --

## **10. Date of revision of text:** April 2019