

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Name of the medicinal product

Ondansetron Orodispersible Tablets 4 mg

Ondansetron Orodispersible Tablets 8 mg

**Product Distribution Category:** "Prescription only medicine"

### 2. Qualitative and quantitative composition

Each Orodispersible Tablet contains 4mg Ondansetron USP.

Each Orodispersible Tablet contains 8mg Ondansetron USP.

List of excipients:

| Excipients   | Quality Referential    | Quantity (%) | Effect                       |
|--|------------------------|--------------|------------------------------|
| Mannitol 35 (Pearlitol 50 C)                         | Ph.Eur.<br>current ed. | 36.54        | Diluent                      |
| Amino Methacrylate Copolymer<br>(Eudragit E100)      | Ph.Eur.<br>current ed. | 0.06         | Binder                       |
| Colloidal silicon dioxide (Aerosil 200)              | Ph.Eur.<br>current ed. | 1.37         | Antistatic agent             |
| Isopropyl alcohol*                                   | Ph.Eur.<br>current ed. | q.s.         | Granulation and coating aid. |
| Mannitol granular (Pearlitol SD 200)                 | Ph.Eur.<br>current ed. | 47.03        | Diluent.                     |
| Kollidone CL<br>(Cross linked polyvinyl pyrrolidone) | Ph.Eur.<br>current ed. | 7.50         | Disintegrant.                |
| Aspartame  | Ph.Eur.<br>current ed. | 1.50         | Sweetener                    |
| Flavor Strawberry                                    | In-House               | 3.00         | Flavouring agent.            |
| Magnesium stearate                                   | Ph.Eur.<br>current ed. | 1.00         | Lubricant.                   |

### 3. Pharmaceutical form

Orodispersible Tablet.

Ondansetron 4 mg Orodispersible Tablets are round white to off-white, flat, bevelled edged tablets, plain on both the surfaces, having strawberry odour, packed in aluminium-aluminium blister.

Ondansetron 8 mg Orodispersible Tablets are round white to off-white, flat, bevelled edged tablets, plain on both the surfaces, having strawberry odour, packed in aluminium-aluminium blister.

#### **4. Clinical particulars**

##### **4.1 Therapeutic indications**

###### **Adults:**

Ondansetron Orodispersible Tablets 4 mg & 8mg is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Ondansetron Orodispersible Tablets 4 mg & 8mg is indicated for the prevention of post-operative nausea and vomiting (PONV).

For treatment of established PONV, administration by injection is recommended.

###### **Paediatric Population:**

Ondansetron Orodispersible Tablets 4 mg & 8mg is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged  $\geq 6$  months

For the prevention and treatment of PONV in children aged  $\geq 1$  month, administration by injection is recommended.

##### **4.2 Posology and method of administration**

Place the orodispersible Tablets on top of the tongue, where it will disperse within seconds, then swallow.

###### **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 selection of dose regimen should be determined by the severity of the emetogenic challenge.

*Emetogenic chemotherapy and radiotherapy:* Ondansetron Orodispersible Tablets 4 mg can be given either by rectal, oral (as Orodispersible Tablets, tablets or syrup) 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 Orodispersible Tablets 4 mg & 8mg 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 Orodispersible Tablets 4 & 8mg mg 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.

***Paediatric Population:***

CINV in children aged  $\geq 6$  months and adolescents

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.

There are no data from controlled clinical trials on the use of Ondansetron Orodispersible Tablets 4 mg & 8mg in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of Ondansetron Orodispersible Tablets 4 mg & 8mg for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron Orodispersible Tablets 4 mg & 8mg should be administered immediately before chemotherapy as a single intravenous dose of  $5 \text{ mg/m}^2$ . The single intravenous dose must not exceed 8 mg.

Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1).

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

Table 1: BSA-based dosing for Chemotherapy - Children aged  $\geq 6$  months and adolescents

| BSA                    | Day 1 (a,b)  | Days 2-6 <sup>(b)</sup>             |
|------------------------|--|-------------------------------------|
| $< 0.6 \text{ m}^2$    | $5 \text{ mg/m}^2$ IV. plus 2 mg syrup after 12 hours          | 2 mg syrup every 12 hours           |
| $\geq 0.6 \text{ m}^2$ | $5 \text{ mg/m}^2$ IV plus 4 mg syrup or tablet after 12 hours | 4 mg syrup or tablet every 12 hours |

|                    |  |                                    |
|--------------------|--|------------------------------------|
| >1.2m <sup>2</sup> | 5mg/m <sup>2</sup> 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 must not exceed adult dose of 32 mg

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing. Ondansetron Orodispersible Tablets 4 mg & 8mg should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The single intravenous dose must not exceed 8 mg. 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 (Table 2).

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

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

| Weight  | Day 1 (a,b)                               | Days 2-6 <sup>(b)</sup>             |
|---------|---|-------------------------------------|
| ≤ 10 kg | Up to 3 doses of 0.15 mg/kg every 4 hours | 2 mg syrup every 12 hours           |
| > 10 kg | Up to 3 doses of 0.15 mg/kg every 4 hours | 4 mg syrup or tablet every 12 hours |

a The intravenous dose must not exceed 8mg.

b The total daily dose must not exceed adult dose of 32 mg.

***Elderly:***

Ondansetron Orally Disintegrating Tablets 4 mg & 8mg 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 Orodispersible Tablets 4 mg & 8mg may be administered either orally (as orally disintegrating tablets, tablets or syrup) or by intravenous or intramuscular injection.

For oral administration: 16mg taken one hour prior to anesthesia.

*For the treatment of established PONV:* Intravenous or intramuscular administration is recommended.

***Paediatric population:***

***PONV in children aged  $\geq 1$  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; slow IV injection (not less than 30 seconds) is recommended for this purpose.

***Injection:***

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 Orodispersible Tablets 4 mg & 8mg 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 are no data on the use of Ondansetron Orodispersible Tablets 4 mg & 8mg in the treatment of PONV in children below 2 years of age.

***Elderly:***

There is limited experience in the use of Ondansetron Orodispersible Tablets 4 mg & 8mg in the prevention and treatment of PONV in the elderly, however Ondansetron Orodispersible Tablets 4 & 8mg mg 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 Orodispersible Tablets 4 mg & 8mg 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/debrisoquinemetabolism:***

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 is required.

**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 QT<sub>c</sub>, 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.

Ondansetron Orodispersible Tablets 4 mg & 8mg formulation contains aspartame and therefore should be taken with caution in patients with phenylketonuria.

*Neither non-clinical nor clinical data are available to assess aspartame use in infant below 12 weeks of age.*

***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 5mg/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 co-administered 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 or 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 the 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 Orodispersible Tablets 4 mg & 8mg should not breast-feed their babies.

## **4.7 Effects on 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 ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1000$ ) and very rare ( $< 1/10,000$ ). Very common, common and uncommon events were generally determined from clinical trial data. 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 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.

## **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 (see section 4.8). 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.

### Treatment

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

### 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 8-12 hrs or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hrs. 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        | $\leq 0.001$ |
| S3GT09 | CR        | 61            | 35        | $\leq 0.001$ |
| S3A381 | CR        | 53            | 17        | $\leq 0.001$ |
| 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 of ondansetron, absorption is rapid with maximum peak plasma concentrations of about 30ng/mL being attained and achieved in approximately 1.5 hours after an 8mg dose. The syrup and tablet formulations are bioequivalent and have an absolute oral bioavailability of 60%. The disposition of ondansetron following oral, intravenous and intramuscular dosing is similar with a terminal elimination half-life of approximately 3 hours and a steady-state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%) and 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 the pharmacokinetics of ondansetron. 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 mL/min), systemic clearance and volume of distribution are reduced, 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.

### *Hepatic impairment*

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 hours) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

## **5.3 Preclinical safety data**

No additional data of relevance.

## **6. Pharmaceutical particulars**

## 6.1 List of excipients

|  |     |
|--|-----|
| Mannitol 35 (Pearlitol 50 C)   | USP |
| Colloidal silicon dioxide (Aerosil 200)  | USP |
| Amino Methacrylate Copolymer (Eudragit E100)   | USP |
| Isopropyl alcohol*   | USP |
| Mannitol granular (Pearlitol SD 200)   | USP |
| Kollidone CL (Cross linked polyvinyl pyrrolidone)  | USP |
| Aspartame  | USP |
| Flavor Strawberry  | IH  |
| <b>(Nature identical flavouring, Natural flavours, Corn Maltodextrin, E 1520 propylene glycol)</b> |     |
| Magnesium stearate   | USP |

\* Solvent does not remain in final product.

## 6.2 Incompatibilities

None reported.

## 6.3 Shelf life

24 months

## 6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

## 6.5 Nature and contents of container

Alu-Alu blister pack of 10 tablets each

## 6.6 Special precautions for disposal and other handling

Not applicable.

## 7. Marketing authorization holder and manufacturing site addresses

Athena Drug Delivery Solutions Pvt. Ltd.

602, 6<sup>th</sup> Floor, STAR HUB, Tower II, Sahar International Airport Road,  
Andheri (East), Mumbai 400059 Maharashtra, India.



**8. Marketing authorization number**

TAN 21 HM 0118

**9. Date Of First <Registration> / Renewal Of The <Registration>**

29/03/2021

**10. Date of revision of the text**

March 2021