Public Assessment Report

Decentralised Procedure

Ondansetron 4mg Orodispersible tablets

Ondansetron 8mg Orodispersible tablets

PL 08553/0275
PL 08553/0276

UK/H/1028/001/DC

Dr. Reddy’s Laboratories (UK) Ltd
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dr. Reddy’s Laboratories (UK) Ltd Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg Orodispersible tablets and Ondansetron 8mg Orodispersible tablets (Product Licence numbers: PL 08553/0275-6). These medicines are available on prescription only.

Ondansetron Orodispersible tablets belong to a group of medicines called serotonin (5HT3) antagonists. Medicines used in the treatment of cancer, radiation therapy or surgical procedures can cause you to be sick or feel sick. Ondansetron Orodispersible tablets are used for the prevention and/or treatment of nausea and vomiting induced by these medicines or surgical procedures.

The data submitted in support of these applications for Ondansetron 4mg and 8mg Orodispersible tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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</table>
**Module 1**

**Information about decentralised procedure**

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Ondansetron 4mg Orodispersible tablets</th>
<th>Ondansetron 8mg Orodispersible tablets</th>
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<td>Level 5 Prescription only</td>
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<td><strong>Pharmaceutical form and strength</strong></td>
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<td><strong>Reference numbers for the decentralised Procedure</strong></td>
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<td><strong>End date of decentralised procedure</strong></td>
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<td>Dr. Reddy’s Laboratories (UK) Ltd</td>
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<tr>
<td></td>
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<td></td>
</tr>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ondansetron 4mg Orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 4 mg of Ondansetron

Excipients:
Also contains 1.85 mg of Aspartame (E951)

For the full list of excipients please refer to Section 6.1

3 PHARMACEUTICAL FORM
Orodispersible tablets

Ondansetron 4mg Orodispersible tablets are white to off-white, round, biconvex, uncoated tablets embossed ‘4’ on one side and ‘O’ on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adults:
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy
Prevention and treatment of post-operative nausea and vomiting.

Paediatric Population:
Management of chemotherapy -induced nausea and vomiting in children aged ≥6 months.
Prevention and treatment of post-operative nausea and vomiting in children aged ≥1 month.

4.2 Posology and method of administration
Place the orodispersible tablets on top of the tongue where it will disperse quickly. Swallow with a glass of water.

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 dose of ondansetron should be flexible and selected as shown below.
Emetogenic chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8 mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

For oral administration 8mg 1-2 hours before treatment followed by 8mg 12 hours later

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for upto 5 days and rectal treatment for upto 3 days after a course of treatment. The recommended dose for oral administration is 8mg twice a day.

Highly emetogenic chemotherapy (e.g. with Cisplatin): For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, ondansetron can be given by, intravenous administration.

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.

The recommended dose for oral administration is 8 mg twice daily

**Paediatric population:**
Chemotherapy-induced nausea and vomiting in children aged ≥6 months and adolescents
The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4 and 5.1).

There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged chemotherapy-induced nausea and vomiting. There are no data from controlled clinical trials on the use of ondansetron for radiotherapy-induced nausea and vomiting in children.

**Dosing by BSA:**
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m². The 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 daily dose must not exceed adult dose of 32 mg.

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

<table>
<thead>
<tr>
<th>BSA</th>
<th>Day 1</th>
<th>Days 2-6</th>
</tr>
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<tbody>
<tr>
<td>&lt; 0.6</td>
<td>5 mg/m²</td>
<td>2 mg syrup every 12</td>
</tr>
</tbody>
</table>
Dosing by bodyweight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4. and 5.1).
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg.
Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.
Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2).

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

<table>
<thead>
<tr>
<th>Weight</th>
<th>Day 1 (^{(a,b)})</th>
<th>Days 2-6 (^{(b)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg every 4 hrs</td>
<td>2 mg syrup every 12 hrs</td>
</tr>
<tr>
<td>&gt;10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg every 4 hrs</td>
<td>4 mg syrup or tablet every 12 hrs</td>
</tr>
</tbody>
</table>

**(a)** The intravenous dose must not exceed 8mg.
**(b)** The total daily dose must not exceed adult dose of 32 mg.

**Elderly:**
Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration is required. Please refer also to “Special populations”.

**Post operative nausea and vomiting**

**Adults:**
For prevention of Post-Operative Nausea and Vomiting (PONV): ondansetron can be administered orally or by intravenous injection.
For oral administration: 16mg 1 hour prior to anaesthesia. Alternatively, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

Treatment of established PONV: intravenous administration is recommended.

**Paediatric population**
PONV in children aged ≥1 month and adolescents
Oral formulations:
No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow i.v. injection is recommended for this purpose. There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

**Elderly:**
There is limited experience with Ondansetron in the prevention and treatment of post operative nausea and vomiting in the elderly. However, Ondansetron is well tolerated in this group of patients receiving chemotherapy. Please refer also to “Special populations”.

**Special Populations:**

- **Patients with renal impairment**
  No alteration of daily dosage or frequency of dosing and route of administration is necessary.

- **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 8 mg should not exceed.

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

**4.3 Contraindications**
Hypersensitivity to ondansetron or any of the excipients. Hypersensitivity to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron).

**4.4 Special warnings and precautions for use**
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

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.

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is co-administered with
anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Caution is advised if patients have received cardiotoxic agents and in patients with a history of prolonged QT syndrome.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Paediatric Population:
Paediatric patients receiving ondansetron with hepatotoxic chemo-therapeutic agents should be monitored closely for impaired hepatic function.

Chemotherapy -induced nausea and vomiting: 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/m2 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 indicate similar efficacy for both regimens – see section 5.1.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ondansetron Orodispensible Tablets contain a source of phenylalanine in the form of aspartame (see section 6.1) which may be harmful to patients with phenylketonuria.

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 medicinal products commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, propofol and thiopental.

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.

Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the 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.
Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. (See section 4.4).

4.6 **Pregnancy and lactation**

**Pregnancy**
The safety of Ondansetron for use in human pregnancy has not been established.
The evaluation of experimental studies in animals does not indicate any direct or indirect damaging effects on 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.

**Lactation**
Tests have shown that Ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving Ondansetron should not breast feed 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.

4.8 **Undesirable effects**
Adverse events are listed below by system organ class and frequency. Frequencies are defined as:
- Very common (>1/10)
- Common (>1/100 and <1/10)
- Uncommon (>1/1000 and <1/100)
- Rare (>1/10,000 and <1/1000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Very rarely transient ECG changes including QT interval prolongation have been reported.

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. There may be cross-sensitivity with other selective 5-HT3 antagonists.

**Nervous system disorders**
Very common: Headache.
Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures.
Rare: Dizziness during i.v. administration

Eye disorders
Rare: Transient visual disturbances (eg. blurred vision) during i.v. administration.
Very rare: Transient blindness predominantly during intravenous administration
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.

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

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests. These events were observed commonly in patients receiving chemotherapy with cisplatin.

The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose
Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8 Undesirable effects).

There is no specific antidote for Ondansetron; therefore in all cases of suspected overdose appropriate symptomatic and support 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 (5HT3) antagonists, ATC code: A04AA01

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located in both 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.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansetron does not alter plasma prolactin concentrations.

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

Paediatric population
Chemotherapy-induced nausea and vomiting
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. On the days of chemotherapy, patients received either ondansetron 5 mg/m² i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. 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/m² i.v. + ondansetron 4 mg p.o.) and 41% (0.45 mg/kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial 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 ad-ministered intravenously at a dose of 5 mg/m² i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8mg + 2- 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups re-ceived 4 mg ondansetron syrup twice daily for 2 days.
The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in open-label, non-comparative, single-arm study. All children received three 0.15 mg/kg doses of intravenous ondansetron, administered at 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.

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

Prevention of post-operative nausea and vomiting:
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).

5.2 Pharmacokinetic properties
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (bioavailability is about 60%). 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. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) 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 explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important.

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 140L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.
The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. 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 has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

**Special Patient Populations**

**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 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 4 to 18 years), and surgical patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.

**Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population (Intravenous Dose)</th>
<th>Age</th>
<th>N</th>
<th>AUC (ng.h/mL)</th>
<th>CL (L/h/kg)</th>
<th>Vd (L/kg)</th>
<th>T1/2 (h)</th>
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<td>S3A403919</td>
<td>Surgery (0.1 or 0.2 mg/kg)</td>
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<td>360</td>
<td>0.401</td>
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<td>S3A40310</td>
<td>Surgery</td>
<td>5 to 24 months</td>
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<td>236</td>
<td>0.581</td>
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MHRA PAR; ONDANSETRON 4MG AND 8MG ORODISPERSIBLE TABLETS, PL 08553/0275-6
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<th>(0.1 or 0.2 mg/kg)</th>
<th>months</th>
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<td>1</td>
<td>1</td>
<td>257</td>
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<tr>
<td>S3KG024</td>
<td>Surgery (2mg or 4mg)</td>
<td>3 to 12 years</td>
<td>2</td>
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<td>S3A-150</td>
<td>Cancer (0.15mg/kg q4h)</td>
<td>4 to 18 years</td>
<td>2</td>
<td>1</td>
<td>247</td>
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1 Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg
2 Population PK Patients: 64% cancer patients and 36% surgery patients
3 Population estimates shown; AUC based on dose of 0.15 mg/kg
4 Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

**Renal impairment**

In patients with renal impairment (creatinine clearance>15 ml/min), systemic clearance and volume of distribution are reduced following IV administration, resulting in a slight, but clinically insignificant increase in elimination half-life (5.4h). 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**

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

### 5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity and carcinogenic potential.

Ondansetron and its metabolites accumulate in the milk of rats at a milk:plasma ratio of 5.2:1. A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Cellulose, microcrystalline (E460)
- Mannitol (E421)
- Starch, pregelatinised maize
- Crospovidone
- Sodium laurilsulfate
- Microcrystalline cellulose and Guar gum (Avicel CE15)
- Aspartame (E951)
- Anhydrous colloidal silica,
Magnesium stearate (E470b)
Strawberry flavouring (maize maltodextrin, propylene glycol [E1520], alpha-tocopherol [E307], flavouring ingredients)

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
Cold formable Aluminium / Aluminium foil, paper backed easily peelable blister strip packed in cartons to contain 6 or 10 tablets.

Do not attempt to push the orodispersible tablets through the lidding foil. Peel back the lidding foil of one blister and gently remove the orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
There are no special requirements for disposal

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0275

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION
19/02/2010

10 DATE OF REVISION OF THE TEXT
19/02/2010

1 NAME OF THE MEDICINAL PRODUCT
Ondansetron 8mg Orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 8 mg of Ondansetron
Excipients:  
Also contains 3.7 mg of Aspartame (E951)

For the full list of excipients please refer to Section 6.1

3 PHARMACEUTICAL FORM
Orodispersible tablets

Ondansetron 8mg Orodispersible tablets are white to off-white, round, biconvex, uncoated tablets embossed ‘8’ on one side and ‘O’ on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adults:  
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy  
Prevention and treatment of post-operative nausea and vomiting.

Paediatric Population:  
Management of chemotherapy -induced nausea and vomiting in children aged ≥6 months.  
Prevention and treatment of post-operative nausea and vomiting in children aged ≥1 month.

4.2 Posology and method of administration
Place the orodispersible tablets on top of the tongue where it will disperse quickly. Swallow with a glass of water.

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 dose of ondansetron should be flexible and selected as shown below.

Emetogenic chemotherapy and Radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8 mg should be administered as a slow intravenous or intramuscular injection immediately before treatment, followed by 8 mg orally twelve hourly.

For oral administration 8mg 1-2 hours before treatment followed by 8mg 12 hours later
To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days and rectal treatment for up to 3 days after a course of treatment. The recommended dose for oral administration is 8mg twice a day.

Highly emetogenic chemotherapy (e.g. with Cisplatin): For patients receiving highly emetogenic chemotherapy, eg. high-dose cisplatin, ondansetron can be given by, intravenous administration.

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.

The recommended dose for oral administration is 8 mg twice daily

**Paediatric population:**
Chemotherapy-induced nausea and vomiting in children aged ≥6 months and adolescents
The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4 and 5.1).
There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged chemotherapy-induced nausea and vomiting. There are no data from controlled clinical trials on the use of ondansetron for radiotherapy-induced nausea and vomiting in children.

**Dosing by BSA:**
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m². The 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 daily dose must not exceed adult dose of 32 mg.

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

<table>
<thead>
<tr>
<th>BSA</th>
<th>Day 1 (a,b)</th>
<th>Days 2-6(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.6 m²</td>
<td>5 mg/m² i.v. plus 2 mg syrup after 12 hrs</td>
<td>2 mg syrup every 12 hrs</td>
</tr>
<tr>
<td>≥ 0.6 m²</td>
<td>5 mg/m² i.v. plus 4 mg syrup or tablet after 12 hrs</td>
<td>4 mg syrup or tablet every 12 hrs</td>
</tr>
</tbody>
</table>

(a) The intravenous dose must not exceed 8mg.
(b) The total daily dose 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 (sections 4.4. and 5.1).

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2).

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

<table>
<thead>
<tr>
<th>Weight</th>
<th>Day 1(^{(a,b)})</th>
<th>Days 2-6(^{(b)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg every 4 hrs</td>
<td>2 mg syrup every 12 hrs</td>
</tr>
<tr>
<td>&gt; 10 kg</td>
<td>Up to 3 doses of 0.15 mg/kg every 4 hrs</td>
<td>4 mg syrup or tablet every 12 hrs</td>
</tr>
</tbody>
</table>

\(^{(a)}\) The intravenous dose must not exceed 8 mg.
\(^{(b)}\) The total daily dose must not exceed adult dose of 32 mg.

**Elderly:**
Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration is required. Please refer also to “Special populations”.

**Post operative nausea and vomiting**

**Adults:**
For prevention of Post-Operative Nausea and Vomiting (PONV): ondansetron can be administered orally or by intravenous injection.
For oral administration: 16mg 1 hour prior to anaesthesia. Alternatively, 8mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

Treatment of established PONV: intravenous administration is recommended.

**Paediatric population**

**PONV in children aged ≥1 month and adolescents**

Oral formulations:
No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow i.v. injection is recommended for this purpose.
There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

**Elderly:**
There is limited experience with Ondansetron in the prevention and treatment of post operative nausea and vomiting in the elderly. However, Ondansetron is
well tolerated in this group of patients receiving chemotherapy. Please refer also to “Special populations”.

Special Populations:

Patients with renal impairment
No alteration of daily dosage or frequency of dosing and route of administration is necessary.

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 8 mg should not exceed.

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

4.3 Contraindications
Hypersensitivity to ondansetron or any of the excipients. Hypersensitivity to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron).

4.4 Special warnings and precautions for use
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

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.

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is co-administered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Caution is advised if patients have received cardiotoxic agents and in patients with a history of prolonged QT syndrome.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.
Paediatric Population:
Paediatric patients receiving ondansetron with hepatotoxic chemo-therapeutic agents should be monitored closely for impaired hepatic function.
Chemotherapy-induced nausea and vomiting: 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/m2 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 indicate similar efficacy for both regimens – see section 5.1.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ondansetron Orodispersible Tablets contain a source of phenylalanine in the form of aspartame (see section 6.1) which may be harmful to patients with phenylketonuria.

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 medicinal products commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, propofol and thiopental.

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.

Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the 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.

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. (See section 4.4).

4.6 Pregnancy and lactation
Pregnancy
The safety of Ondansetron for use in human pregnancy has not been established.
The evaluation of experimental studies in animals does not indicate any direct or indirect damaging effects on 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.

**Lactation**
Tests have shown that Ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving Ondansetron should not to breast feed 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.

4.8 **Undesirable effects**
Adverse events are listed below by system organ class and frequency. Frequencies are defined as:
- Very common (>1/10)
- Common (>1/100 and <1/10)
- Uncommon (>1/1000 and <1/100)
- Rare (>1/10,000 and <1/1000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

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.

Very rarely transient ECG changes including QT interval prolongation have been reported.

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. There may be cross-sensitivity with other selective 5-HT3 antagonists.

**Nervous system disorders**
Very common: Headache.
Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures.
Rare: Dizziness during i.v. administration

**Eye disorders**
Rare: Transient visual disturbances (eg. blurred vision) during i.v. administration.
Very rare: Transient blindness predominantly during intravenous administration
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.

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

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests. These events were observed commonly in patients receiving chemotherapy with cisplatin.

The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose
Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8 Undesirable effects).

There is no specific antidote for Ondansetron; therefore in all cases of suspected overdose appropriate symptomatic and support 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 (5HT3) antagonists, ATC code: A04AA01
Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located in both 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.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansetron does not alter plasma prolactin concentrations.

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

**Paediatric population**

Chemotherapy-induced nausea and vomiting

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. On the days of chemotherapy, patients received either ondansetron 5 mg/m2 i.v. + after 8-12 hrs ondansetron 4 mg p.o. or ondansetron 0.45 mg/kg i.v. + after 8-12 hrs placebo p.o. 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/m2 i.v. + ondansetron 4 mg p.o.) and 41% (0.45 mg/kg i.v. + placebo p.o.). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days.

A double-blind randomised placebo-controlled trial 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 ad-ministered intravenously at a dose of 5 mg/m2 i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8mg + 2-4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups re-ceived 4 mg ondansetron syrup twice daily for 2 days.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in open-label, non-comparative, single-arm study. All children received three 0.15 mg/kg doses of intravenous ondansetron, administered at 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.
Another open-label, non-comparative, single-arm study investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4mg for children aged < 12 yrs and 8 mg for children aged ≥ 12 yrs (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

**Prevention of post-operative nausea and vomiting:**
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).

5.2 **Pharmacokinetic properties**

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (bioavailability is about 60%). 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. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) 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 explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important.

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 140L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. 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 has no
effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

**Special Patient Populations**

*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 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 4 to 18 years), and surgical patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.

Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population (Intravenous Dose)</th>
<th>Age</th>
<th>N</th>
<th>AUC (ng.h/mL)</th>
<th>CL (L/h/kg)</th>
<th>VdH (L/kg)</th>
<th>T2/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3A403919</td>
<td>Surgery (0.1 or 0.2 mg/kg)</td>
<td>1 to 4 months</td>
<td>1 9</td>
<td>360</td>
<td>0.401</td>
<td>3.5</td>
<td>6.7</td>
</tr>
<tr>
<td>S3A40319†</td>
<td>Surgery (0.1 or 0.2 mg/kg)</td>
<td>5 to 24 months</td>
<td>2 2</td>
<td>236</td>
<td>0.581</td>
<td>2.3</td>
<td>2.9</td>
</tr>
<tr>
<td>S3A40320 &amp; S3A40319</td>
<td>Cancer/Surgery (0.15mg/kg q4h/0.1 or</td>
<td>1 to 48 months</td>
<td>1 1 5</td>
<td>257</td>
<td>0.582</td>
<td>3.65</td>
<td>4.9</td>
</tr>
<tr>
<td>Pop PK(^{2,3}) 0.2mg/kg)</td>
<td>Surgery (2mg or 4mg)</td>
<td>3 to 12 years</td>
<td>2</td>
<td>240</td>
<td>0.439</td>
<td>1.65</td>
<td>2.9</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----</td>
</tr>
<tr>
<td>S3K024(^4)</td>
<td>Cancer (0.15mg/kg q4h)</td>
<td>4 to 18 years</td>
<td>2</td>
<td>247</td>
<td>0.599</td>
<td>1.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

1 Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg
2 Population PK Patients: 64% cancer patients and 36% surgery patients
3 Population estimates shown; AUC based on dose of 0.15 mg/kg
4 Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

**Renal impairment**
In patients with renal impairment (creatinine clearance>15 ml/min), systemic clearance and volume of distribution are reduced following IV administration, resulting in a slight, but clinically insignificant increase in elimination half-life (5.4h). 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**
In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32h) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

### 5.3 Preclinical safety data
Preclinical data revealed no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity and carcinogenic potential.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
- Cellulose, microcrystalline (E460)
- Mannitol (E421)
- Starch, pregelatinised maize
- Crospovidone
- Sodium laurilsulfate
- Microcrystalline cellulose and Guar gum (Avicel CE15)
- Aspartame (E951)
- Anhydrous colloidal silica,
- Magnesium stearate (E470b)
- Strawberry flavouring (maize maltodextrin, propylene glycol [E1520], alpha-tocopherol [E307], flavouring ingredients)
6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
None.

6.5 Nature and contents of container
Cold formable Aluminium / Aluminium foil, paper backed easily peelable blister strip packed in cartons to contain 6 or 10 tablets.

Do not attempt to push the orodispersible tablets through the lidding foil. Peel back the lidding foil of one blister and gently remove the orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
There are no special requirements for disposal

7 MARKETING AUTHORISATION HOLDER
Dr. Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD

8 MARKETING AUTHORISATION NUMBER(S)
PL 08553/0276

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Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER
Ondansetron 4mg and 8mg Orodispersible Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT ONDANSETRON ORODISPERSIBLE TABLETS ARE AND WHAT THEY ARE USED FOR
2. BEFORE YOU TAKE ONDANSETRON ORODISPERSIBLE TABLETS
3. HOW TO TAKE ONDANSETRON ORODISPERSIBLE TABLETS
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE ONDANSETRON ORODISPERSIBLE TABLETS
6. FURTHER INFORMATION

1. WHAT ONDANSETRON ORODISPERSIBLE TABLETS ARE AND WHAT THEY ARE USED FOR
Ondansetron Orodispersible Tablets contain ondansetron, which belongs to a group of medicines called serotonin (5HT3) antagonists. Medicines used in the treatment of cancer, radiation therapy or surgical procedures, can cause you to be sick or feel sick (nausea and vomiting). Ondansetron Orodispersible Tablets are used for the prevention and/or treatment of nausea and vomiting induced by these medicines or surgical procedures.

2. BEFORE YOU TAKE ONDANSETRON ORODISPERSIBLE TABLETS
Do not take Ondansetron Orodispersible Tablets
- If you are allergic to ondansetron or any of the other ingredients of the tablets listed in Section 6 or have ever had an allergic reaction to other anti-emetics (such as granisetron or dolasetron)
- If you are pregnant or you are breast feeding.

Taking special care with Ondansetron Orodispersible Tablets
You should consult your doctor before taking Ondansetron Orodispersible Tablets if you have:
- a blockage in your gut or you have severe constipation
- liver disease
- ever had heart problems or an uneven heart beat (arrhythmias)
- surgery scheduled to remove adenoids or tonsils
- problems with levels of salts in your blood, such as potassium, sodium and magnesium.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Are you taking any of the following medicines?
- Phenytin (for seizures),
- Carbamazepine (for seizures, bipolar disorder, shockingly pains in the face – trigeminal neuralgia)
- Rifampicin (used in bacterial infections, for tuberculosis and leprosy treatment)
- Anti-arrhythmic medicines or beta blockers which are used to treat heart problems
- Medicines such as antacids which may increase the risk of irregular heartbeat while you take ondansetron
- Tramadol (for moderate to severe pain)

Please inform your doctor of these before taking ondansetron.

3. HOW TO TAKE ONDANSETRON ORODISPERSIBLE TABLETS
Your doctor will advise you on when and how many Ondansetron Orodispersible Tablets you should take. Always take Ondansetron Orodispersible Tablets as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Do not try to push the tablets through the blister. The tablets are fragile and this can cause the tablets to break. There is a layer of paper on the blister, which should be peeled back to reveal the tablets. The tablets can then be placed on the tongue to disintegrate rapidly. Swallow with water

For treatment of nausea and vomiting caused by cancer chemotherapy or radiotherapy:
The recommended adult dose is 8mg 1 to 2 hours before start of cancer therapy followed by 8mg 12 hours later. To prevent nausea and vomiting after 24 hours of cancer therapy, take 8mg twice daily for up to 3 days.
Children aged over 6 months and adolescents, your doctor will decide the dose based on the age and size or body weight of the child. Ondansetron should not be given to children below 6 months or children who are very small. Please ensure that you take the tablets as recommended by your doctor.
For prevention of nausea and vomiting after surgical procedures:
The usual adult dose is 1 Ihrg one hour prior to anaesthesia or 8mg before and after the operation, then two further doses of 8mg at eight hour intervals.
Children (aged 1 month and over) and adolescents (under 18 years old). The doctor may decide to give an injection rather than tablets.

Patients with liver problems
If you have liver problems, your dose of Ondansetron Orodispersible Tablets should not exceed 8mg per day.
If you are taking or have taken tests to check your liver function, Ondansetron Orodispersible Tablets may affect the results of these tests.

If you take more Ondansetron Orodispersible Tablets than you should
If you have accidentally taken more tablets than you should, contact your doctor or the nearest hospital immediately. Take this leaflet and the pack of Ondansetron Orodispersible Tablets with you, if you can.

If you forget to take Ondansetron Orodispersible Tablets
If you forget to take the tablets, take one as soon as possible. If you have missed a dose but do not feel sick or do not vomit, take the next at the usual time recommended by your doctor. If you are sick (vomiting) within one hour of taking the dose take the dose again.

If you stop taking Ondansetron Orodispersible Tablets
No special precautions are necessary when you stop taking Ondansetron Orodispersible Tablets.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Ondansetron Orodispersible Tablets may cause side effects, although not everybody gets them. Many side effects are usually mild and the side effects go away when you stop taking Ondansetron Orodispersible Tablets. The side effects include:

Very common (seen in more than 1 in 10 people):
- Headache
- Common (seen in less than 1 in 10 people but not in more than 1 in 100 people):
- Sensation of warmth or flushing
- Constipation
- Changes in liver functions test results

Uncommon (seen in less than 1 in 100 people but not in more than 1 in 1000 people):
- Faint, abnormal muscle movements or muscle stiffness, upward rolling of eyes, slow or irregular heartbeat, low blood pressure, chest pain and an increase in liver function tests (most often in patients receiving chemotherapy with cisplatin). Contact your doctor as soon as possible if any of these side effects are seen.
- Nausea

Rare (seen in less than 1 in 1000 people but not in more than 1 in 10,000 people):
- Hypersensitivity reactions including sudden chest pain, wheeziness, swelling of eyelids, face, lips or tongue, skin rashes, hives or red spots. Seek medical attention immediately if any or all of these signs are seen. Visual disturbances e.g. blurred vision (though this has almost always been associated with an ondansetron injection, rather than tablets).
- Rarely dizziness has been observed but only when Ondansetron is administered by the intravenous route.

Very rare (seen in less than 1 in 10,000 people):
- Temporary loss of vision may occur very rarely and is seen mostly during intravenous administration and usually chemotherapy containing cisplatin. It usually goes away in about 20 minutes.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ONDANSETRON ORODISPERSIBLE TABLETS
Keep out of the reach and sight of children.
Do not use Ondansetron Orodispersible Tablets after the expiry date which is stated on the carton and the blister after (EXP). The expiry date refers to the last day of that month. Do not use this medicine if there are signs of deterioration such as discolouration or crumbling. If this medicine appears to be deteriorating, return the pack and all its contents to your pharmacist and ask for a replacement.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Ondansetron Orodispersible Tablets contain
The active substance is Ondansetron (4mg or 8mg).
The other ingredients are: Microcrystalline Cellulose (E460), Mannitol (E421), Starch, Pregeletinised maize, Crospovidone, Sodium Laurilsulfate, Microcrystalline Cellulose and Guar gum (Avicel CE15), Apsparame (E951), Anhydrous Colloidal Silica, Magnesium Stearate (E470b), Strawberry flavouring (maize maltodextrin, propylene glycol (E1520), alpha-tocopheryl) (E307), flavouring ingredients.

What Ondansetron Orodispersible Tablets look like and contents of the pack
Ondansetron 4mg Orodispersible Tablets are white and round in shape, marked with “O” on one side and “4” on other side.
Ondansetron 8mg Orodispersible Tablets are white and round in shape, marked with “O” on one side and “8” on other side.
Ondansetron Orodispersible Tablets are packed in blister strips in cartons.
The blister strips have an outer layer of paper, which when peeled, will reveal the tablets.
The cartons contain 6 or 10 tablets. Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer
Dr. Reddy’s Laboratories UK Ltd. 6 Riverview Road, Beverley, HU17 0LD, UK.

This medicine is also licensed in the EEA under the following names: Ondansetron Dr. Reddy’s 4mg e 8mg Comprese Orodispersibili

Date of preparation: 12/2009
Module 4

Labelling

4 mg tablets

Blister:

Ondansetron 4mg Orodispersible Tablets
Dr. Reddy’s Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 4mg Orodispersible Tablets
Dr. Reddy’s Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 4mg Orodispersible Tablets
Dr. Reddy’s Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 4mg Orodispersible Tablets
Dr. Reddy’s Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 4mg Orodispersible Tablets
Dr. Reddy’s Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.
Each orodispersible tablet contains 4mg of ondansetron. Contains aspartame (E951). Read the package leaflet before use. For Oral Use. Place the tablet on your tongue, then swallow with water. Take as directed by your doctor.
8 mg tablets

Blister:

Ondansetron 8mg Orodispensible Tablets
Dr. Reddy's Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 8mg Orodispensible Tablets
Dr. Reddy's Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 8mg Orodispensible Tablets
Dr. Reddy's Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.

Ondansetron 8mg Orodispensible Tablets
Dr. Reddy's Laboratories (UK) Ltd
Peel back the paper layer. Do not push the tablet through the blister.
Each orodispersible tablet contains 8mg of ondansetron. Contains aspartame (E951). Read the package leaflet before use. For Oral Use. Place the tablet on your tongue, then swallow with water. Take as directed by your doctor.
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Ondansetron 4mg Orodispersible tablets and Ondansetron 8mg Orodispersible tablets as anti-emetics are approvable.

EXECUTIVE SUMMARY
Problem statement
This is an abridged application for marketing authorisation of Ondansetron orodispersible tablets via the decentralised procedure. The UK is the Reference Member State. Ondansetron tablets were first granted approval in the UK in December 1993.

About the product
Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. It is an anti-emetic. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron has been shown to block the initiation of this reflex.

General Comments on the submitted dossier
The application is in accordance with Article 10 (b) Directive 2001/83EC. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements.

The applicant has submitted one bioequivalence study performed under fasting conditions.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence, no increase in environmental risk is to be expected compared to that of the reference product.

No Risk Management Plan other than documentation of pharmacovigilance system has been provided. For generics this is acceptable, since the innovator product is not subject to specific risk management measures.

The applicant has performed user readability testing of the Patient Information Leaflet and the results are satisfactory.

General Comments on Compliance with GMP, GLC, GCP and agreed ethical principle
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent
authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

Since a non-clinical literature review has been presented, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

No issues regarding GCP aspects have been identified during the review of this dossier.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to ondansetron are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications are generally acceptable for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed and the results provided show that the tablets meet the specification proposed, except for the description of the markings on the tablets.

The conditions used in the stability studies are according to the ICH stability guidelines. The proposed shelf-life of 3 years with the no special precautions for storage can be considered acceptable.

Non clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron are well known. As ondansetron is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. A literature-based overview is, therefore, appropriate and there are no non-clinical issues arising from the inclusion of ondansetron in the proposed formulation.
The non-clinical overview, which is dated 13 of March 2007, cites 16 references up to 2003.

Clinical aspects
Bioequivalence
The applicant has submitted one bioequivalence performed under fasting conditions. This was a randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Ondansetron 8mg Orodispensible tablets and Zofran® Melt 8 mg of GlaxoSmithKline UK in healthy human adult subjects, under fasting conditions.

Thirty-five healthy human adult subjects were enrolled in the study and 34 subjects completed the study. One subject was withdrawn from the study due to inter current illness. Blood samples were collected at frequent intervals up to 24 post dosing. There was a 7 day wash out period.

Statistical evaluation was performed using Analysis of Variance (ANOVA). The log-transformed pharmacokinetic parameters (Cmax, AUC0, AUC0-∞) were analyzed using GLM ANOVA model with the main effects of treatment, period and sequence as fixed effects and subjects nested within sequence as random effect. A separate ANOVA model was used to analyze each of the parameters. The sequence effect was tested at the 0.10 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. All other main effects will be tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

Each analysis of variance included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses were done using the appropriate SAS® procedure. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the difference between drug formulation least-square means (LSM) was calculated for the parameters AUC0-t, AUC0-∞ and Cmax. using log-transformed data. The confidence intervals was expressed as a percentage relative to the LSM of the reference formulation. The pharmacokinetic parameters are summarised in the tables below.

Summary of Pharmacokinetic Parameters for Ondansetron (n=34)

<table>
<thead>
<tr>
<th>Test Drug (A) Parameters</th>
<th>Geometric Mean</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>38.126</td>
<td>41.368</td>
<td>18.501</td>
<td>44.72</td>
</tr>
<tr>
<td>Tmax (Hours)</td>
<td>-</td>
<td>1.81</td>
<td>0.59</td>
<td>32.28</td>
</tr>
<tr>
<td>AUC0-t(ng.hr/mL)</td>
<td>256.051</td>
<td>281.203</td>
<td>139.577</td>
<td>49.64</td>
</tr>
<tr>
<td>AUC0-∞(ng.hr/mL)</td>
<td>270.320</td>
<td>298.550</td>
<td>150.575</td>
<td>50.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference Drug (B) Parameters</th>
<th>Geometric Mean</th>
<th>Mean</th>
<th>SD</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>Test</td>
<td>Reference</td>
<td>% Ratio (A/B)</td>
<td></td>
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<tr>
<td>--------------</td>
<td>------</td>
<td>-----------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>37.20</td>
<td>94.93% to 110.23%</td>
<td>102.29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39.941</td>
<td>99.28% to 99.28%</td>
<td>99.28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.247</td>
<td>91.16% to 106.35%</td>
<td>98.47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax (Hours)</td>
<td>-</td>
<td>1.92</td>
<td>36.87</td>
<td></td>
</tr>
<tr>
<td>AUC0-t(ng.hr/mL)</td>
<td>257.901</td>
<td>280.613</td>
<td>45.39</td>
<td></td>
</tr>
<tr>
<td>AUC0-∞(ng.hr/mL)</td>
<td>274.533</td>
<td>301.701</td>
<td>48.57</td>
<td></td>
</tr>
</tbody>
</table>

The 90% confidence intervals of the relative mean AUC and Cmax of the test to reference products for the measured data were within the 80-125% confidence intervals.

There was only one adverse event reported in the study. This was intercurrent illness (acute otitis media) and was assessed as unrelated to study medication.

The essentially linear pharmacokinetics of ondansetron makes it likely that the lower 4mg dose of ondansetron is also bioequivalent to the corresponding marketed brand formulation, although bioequivalence has not been assessed explicitly. Therefore, the bioequivalence of the generic product with the referenced innovator product, marketed in the UK by GlaxoSmithKline has been proven.

**Conclusion**

The highly selective 5HT3 receptor-antagonists, including ondansetron, have been available in the EU for over 10 years. The use of ondansetron is well established. It has recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted. When used as indicated, ondansetron has a favourable benefit-to-risk ratio.