Public Assessment Report

Decentralised Procedure

ONDANSETRON 4MG FILM-COATED TABLETS
ONDANSETRON 8MG FILM-COATED TABLETS

Procedure No: UK/H/1338-9/001-2/DC

UK Licence No: PL 04416/0875-8

Sandoz Limited
LAY SUMMARY

On 12\textsuperscript{th} January 2010, the MHRA granted Sandoz Limited Marketing Authorisations (licences) for the medicinal products Ondansetron 4mg and 8mg Film-Coated Tablets (PL 04416/0875-8). These are prescription-only medicines (POM) that are used for:

- Preventing nausea (feeling sick) and vomiting (being sick) caused by chemotherapy or radiotherapy for cancer in adults and in children aged $\geq 6$ months.
- Preventing nausea and vomiting after surgery in adults and in children aged $\geq 1$ month.

The active ingredient ondansetron belongs to a group of medicines called anti-emetics, drugs against feeling sick (nausea) or being sick (vomiting).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ondansetron 4mg and 8mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure Page 3
Module 2: Summary of Product Characteristics Page 4
Module 3: Product Information Leaflets Page 22
Module 4: Labelling Page 24
Module 5: Scientific Discussion Page 28
   1 Introduction
   2 Quality aspects
   3 Non-clinical aspects
   4 Clinical aspects
   5 Overall conclusions

Module 6 Steps taken after initial procedure
# Module 1

| **Product Name**       | Ondansetron 4mg Film-Coated Tablets  
|                        | Ondansetron 8mg Film-Coated Tablets  
| **Type of Application**| Generic, Article 10.1                
| **Active Substances**  | Ondansetron                           
| **Form**               | Film-coated tablet                    
| **Strength**           | 4mg and 8mg Film-Coated Tablets       
| **MA Holder**          | Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE, United Kingdom  
| **Reference Member State (RMS)** | UK                                      
| **CMS**                | UK/H/1338/001-2/DC – Germany, Ireland, Italy and Luxembourg  
|                        | UK/H/1339/001-2/DC – Austria, Germany and Poland  
| **Procedure Number**   | UK/H/1338-9/001-2/DC                  
| **Timetable**          | Day 210 – 11th December 2009          |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ondansetron 4 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Ondansetron 4 mg Film-coated Tablets:
Each tablet contains ondansetron 4mg (as ondansetron hydrochloride dihydrate).
Excipients :Each tablet contains 74.25 mg lactose as lactose anhydrous and lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet. Yellow, film-coated oval shaped tablets, plain on both sides.

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 (PONV).

Paediatric Population:

4.2 Posology and method of administration
Oral use.

Chemotherapy and radiotherapy induced nausea and vomiting

Adults:
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of ondansetron should be flexible in the range of 8-32 mg a day 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 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 after a course of treatment.

The recommended dose for oral administration is 8mg twice daily.

Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g. 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 doing results in higher total daily doses compared to BSA-based dosing – see sections 4.4.and 5.1.
There are no data from controlled clinical trials on the use of ondansetron in the prevention of chemotherapy-induced delayed or prolonged 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 5mg/m². The intravenous dose must not exceed 8mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.

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 – see sections 4.4. and 5.1.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15mg/kg. The intravenous dose must not exceed 8mg.

Two further doses 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. See Table 2 below.

**Elderly:**
No alteration of dosage, dosing frequency or route of administration are required.

Please refer also to ‘Special populations’.

**Post operative nausea and vomiting (PONV):**

**Adults:**
*For the prevention of PONV:* Ondansetron can be administered orally or by intravenous injection.
For oral administration: 16 mg one hour prior to anaesthesia. Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

*For the treatment of established PONV:* Intravenous administration is recommended.
Paediatric population

Post-operative nausea and vomiting 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.

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 may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There are no data on the use of ondansetron for the treatment of postoperative vomiting in children under 2 years of age.

Elderly:

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly.

Please refer also to ‘Special populations’.

Special populations:

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:

Clearance of ondansetron is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

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 are required.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Ondansetron is not indicated for prevention and treatment of post-operative nausea and vomiting in children after intra-abdominal surgery.

After adenotonsillar surgery antiemetics may mask occult bleeding by preventing vomiting. Therefore, such patients should be followed carefully after ondansetron.

Ondansetron film-coated tablets should not be used in children with a total body surface below 0.6 m².

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 chemotherapeutic 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 medicine contains lactose.

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

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 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.

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:
Data on a limited number of exposed pregnancies indicate no adverse reactions of ondansetron on pregnancy or on the health of the fetus/new-born infant. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal 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. It is therefore recommended that mothers receiving ondansetron 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. 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, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. 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 according to indication and formulation.

Immune system disorders:
Rare: Immediate hypersensitivity reactions, sometimes severe including anaphylaxis. Anaphylaxis may be fatal.
Hypersensitivity reactions were also observed in patients who were sensitive to other selective 5-HT3 antagonists.

Nervous system disorders:
Very common: Headache.
Uncommon: Seizures, movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae.
Rare: Dizziness during i.v. administration, which in most cases is prevented or resolved by lengthening the infusion period.

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.

Investigations:
Uncommon: Asymptomatic increase in liver function tests.

Paediatric population:
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. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. 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 antiemetic action of ondansetron itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04A A01

Ondansetron is a potent, highly selective 5HT3 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 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 both in the peripheral and central nervous system. The mechanisms of action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

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 administered 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 received 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. Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. 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, 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).

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 l. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

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

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

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

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100 ml/min at 3 years. Volume of distribution fell from about 75 l at 12 years to 17 l at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). 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.

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron’s systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.
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>VdSS (L/kg)</th>
<th>T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Geometric Mean</td>
<td>Mean</td>
<td>Mean</td>
<td>Geometric Mean</td>
</tr>
<tr>
<td>S3A40319</td>
<td>Surgery (0.1 or 0.2mg/kg)</td>
<td>1 to 4 months</td>
<td>19</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 0.2mg/kg)</td>
<td>5 to 24 months</td>
<td>22</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 0.2mg/kg)</td>
<td>1 to 48 months</td>
<td>115</td>
<td>257</td>
<td>0.582</td>
<td>3.65</td>
<td>4.9</td>
</tr>
<tr>
<td>S3KG02</td>
<td>Surgery (2 mg or 4 mg)</td>
<td>3 to 12 years</td>
<td>21</td>
<td>240</td>
<td>0.439</td>
<td>1.65</td>
<td>2.9</td>
</tr>
<tr>
<td>S3A-150</td>
<td>Cancer (0.15mg/kg q4h)</td>
<td>4 to 18 years</td>
<td>21</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)

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
Core
lactose anhydrous,  
cellulose microcrystalline,  
starch pregelatinised (maize),  
magnesium stearate

Coat
hydrocollose,  
lactose monohydrate,  
titanium dioxide (E171),  
triacetin,  
iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PVDC/Aluminium blisters.

Pack sizes:
Blister containing 6, 8, 10, 12, 15, 20, 30, 50, 60 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Sandoz Ltd
37 Woolmer Way
Bordon
Hampshire
GU35 9QE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/0875
PL 04416/0877

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/01/2010

10 DATE OF REVISION OF THE TEXT
12/01/2010
1 NAME OF THE MEDICINAL PRODUCT
Ondansetron 8 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Ondansetron 8 mg Film-coated Tablets:
Each tablet contains ondansetron 8mg (as ondansetron hydrochloride dihydrate).
Excipients :Each tablet contains 148 mg lactose as lactose anhydrous and lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet. Yellow, film-coated oval shaped tablets, plain on both sides.

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 (PONV).
Paediatric Population:

4.2 Posology and method of administration
Oral use.

Chemotherapy and radiotherapy induced nausea and vomiting
Adults:
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of ondansetron should be flexible in the range of 8-32 mg a day 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 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 after a course of treatment.

The recommended dose for oral administration is 8mg twice daily.

Highly Emetogenic Chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g. 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 doing results in higher total daily doses compared to BSA-based dosing – see sections 4.4.and 5.1.
There are no data from controlled clinical trials on the use of ondansetron in the prevention of chemotherapy-induced delayed or prolonged 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 5mg/m². The intravenous dose must not exceed 8mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days. See Table 1 below.

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 1a,b</th>
<th>Days 2-6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.6m²</td>
<td>5 mg/m² i.v.</td>
<td>2 mg syrup or tablet after 12 hours</td>
</tr>
<tr>
<td>&gt; 0.6m²</td>
<td>5 mg/m² i.v.</td>
<td>4 mg syrup or tablet after 12 hours</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 – see sections 4.4. and 5.1.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15mg/kg. The intravenous dose must not exceed 8mg.

Two further doses 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. See Table 2 below.

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

<table>
<thead>
<tr>
<th>Weight</th>
<th>Day 1a,b</th>
<th>Days 2-6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10kg</td>
<td>Up to 3 doses of 0.15mg/kg at 4-hourly intervals.</td>
<td>2 mg syrup or tablet every 12 hours</td>
</tr>
<tr>
<td>&gt; 10kg</td>
<td>Up to 3 doses of 0.15mg/kg at 4-hourly intervals.</td>
<td>4 mg syrup or tablet every 12 hours</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:
No alteration of dosage, dosing frequency or route of administration are required.

Please refer also to ‘Special populations’.

Post operative nausea and vomiting (PONV):
Adults:
For the prevention of PONV: Ondansetron can be administered orally or by intravenous injection. For oral administration: 16 mg one hour prior to anaesthesia. Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8mg at eight hourly intervals.

For the treatment of established PONV: Intravenous administration is recommended.
Paediatric population

Post-operative nausea and vomiting in children aged $\geq 1$ 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.

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 may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There are no data on the use of ondansetron for the treatment of postoperative vomiting in children under 2 years of age.

Elderly:
There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly.

Please refer also to ‘Special populations’.

Special populations:

Patients with renal impairment:
No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment:
Clearance of ondansetron is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8mg should not be exceeded.

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 are required.

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

4.4 Special warnings and precautions for use
Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Ondansetron is not indicated for prevention and treatment of post-operative nausea and vomiting in children after intra-abdominal surgery.

After adenotonsillar surgery antiemetics may mask occult bleeding by preventing vomiting. Therefore, such patients should be followed carefully after ondansetron.

Ondansetron film-coated tablets should not be used in children with a total body surface below 0.6 m².

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 chemotherapeutic 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 medicine contains lactose.

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

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 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.

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:
Data on a limited number of exposed pregnancies indicate no adverse reactions of ondansetron on pregnancy or on the health of the fetus/new-born infant. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal 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. It is therefore recommended that mothers receiving ondansetron 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. 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, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. 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 according to indication and formulation.

**Immune system disorders:**
Rare: Immediate hypersensitivity reactions, sometimes severe including anaphylaxis. Anaphylaxis may be fatal.

Hypersensitivity reactions were also observed in patients who were sensitive to other selective 5-HT3 antagonists.

**Nervous system disorders:**
Very common: Headache.

Uncommon: Seizures, movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae.

Rare: Dizziness during i.v. administration, which in most cases is prevented or resolved by lengthening the infusion period.

**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. Patients with signs of subacute obstruction should be monitored.

**Hepatobiliary disorders:**
Uncommon: Asymptomatic increase in liver function tests#.

#These events were observed commonly in patients receiving chemotherapy with cisplatin.

**Investigations:**
Uncommon: Asymptomatic increase in liver function tests.

**Paediatric population:**
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. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. 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 antiemetic action of ondansetron itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04A A01

Ondansetron is a potent, highly selective 5HT3 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 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 both in the peripheral and central nervous system. The mechanisms of action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

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 administered 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 received 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. Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8mg dose. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. 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, 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).

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 l. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

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

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

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

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100 ml/min at 3 years. Volume of distribution fell from about 75 l at 12 years to 17 l at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). 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.

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron’s systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.
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>VdSS (L/kg)</th>
<th>T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Mean</td>
<td>Mean</td>
<td>Geometric Mean</td>
<td>Mean</td>
<td>Geometric Mean</td>
<td>Mean</td>
<td>Geometric Mean</td>
</tr>
<tr>
<td>S3A40319①</td>
<td>Surgery (0.1 or 0.2mg/kg)</td>
<td>1 to 4 months</td>
<td>19</td>
<td>360</td>
<td>0.401</td>
<td>3.5</td>
<td>6.7</td>
</tr>
<tr>
<td>S3A40319①</td>
<td>Surgery (0.1 or 0.2mg/kg)</td>
<td>5 to 24 months</td>
<td>22</td>
<td>236</td>
<td>0.581</td>
<td>2.3</td>
<td>2.9</td>
</tr>
<tr>
<td>S3A40320 &amp; S3A40319 Pop PK②,③</td>
<td>Cancer/Surgery (0.15mg/kg q4h/0.1 or 0.2mg/kg)</td>
<td>1 to 48 months</td>
<td>115</td>
<td>257</td>
<td>0.582</td>
<td>3.65</td>
<td>4.9</td>
</tr>
<tr>
<td>S3KG02④</td>
<td>Surgery (2 mg or 4 mg)</td>
<td>3 to 12 years</td>
<td>21</td>
<td>240</td>
<td>0.439</td>
<td>1.65</td>
<td>2.9</td>
</tr>
<tr>
<td>S3A-150</td>
<td>Cancer (0.15mg/kg q4h)</td>
<td>4 to 18 years</td>
<td>21</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)

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
Core
lactose anhydrous,
cellulose microcrystalline,
starch pregelatinised (maize),
magnesium stearate

Coat
hypromellose,
lactose monohydrate,
titanium dioxide (E171),
triacetin,
iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/PVDC//Aluminium blisters.

Pack sizes:
Blisters containing 6, 8, 10, 12, 15, 20, 30, 50, 60 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Sandoz Ltd
37 Woolmer Way
Bordon
Hampshire
GU35 9QE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/0876
PL 04416/0878

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/01/2010

10 DATE OF REVISION OF THE TEXT
12/01/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ondansetron 4 mg Film-coated Tablets
Ondansetron 8 mg Film-coated Tablets

Ondansetron (as hydrochloride dihydrate)

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 gets 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 Tablets are and what they are used for
2. Before you take use Ondansetron Tablets
3. How to take Ondansetron Tablets
4. Possible side effects
5. How to store Ondansetron Tablets
6. Further information

1. What Ondansetron Tablets are and what they are used for

Ondansetron belongs to a group of medicines called anti-emetics, drugs against feeling sick
(nausea) or being sick (vomiting).

This medicine is used for
- Preventing nausea (feeling sick) and vomiting (being sick) caused by chemotherapy or
radiotherapy for cancer in adults and in children aged ≥ 6 months.
- Preventing nausea and vomiting after surgery in adults and in children aged ≥ 1 month.

2. Before you take Ondansetron Tablets

Ondansetron Tablets are not suitable for everyone.

Do not use Ondansetron Tablets if you are allergic (hypersensitive) to:
- ondansetron
- similar medicines to ondansetron such as granisetron or dolasetron
- any of the other ingredients of Ondansetron Tablets (see section 6)
Ask your doctor or pharmacist if you are not sure about anything before you take Ondansetron Tablets.

Take special care with Ondansetron Tablets and tell your doctor:
- if you suffer from any blockage in your gut or if you have severe constipation
- if you have liver problems
- if you are having your tonsils out
- if you have a heart problem or are taking medicines used to treat a heart problem
- if your child is being treated with medicines which are toxic to the liver, he/she should be closely monitored for damaged liver function.

This medicine should not be used in children under 2 years of age, or in very small children, because insufficient experience is available.

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.
- If you are taking phenytoin, carbamazepin (used to treat epilepsy or other illnesses), or rifampicin (used to treat certain infections): the ondansetron blood concentrations are decreased.
- If you are taking tramadol (used to treat pain): the effect of tramadol may be reduced.
- If you are taking medicines used to treat heart problems (anti-arrhythmics and/or betablockers)
- If you are taking medicines which are known to have toxic effects on the heart. These medicines may not be used together with ondansetron as they may increase the risk of irregular heartbeat.

Pregnancy and breast-feeding
- Because of insufficient experience the use of ondansetron during pregnancy is not recommended.
- Ondansetron enters the breast milk, so you should not breastfeed while you are having this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ondansetron has no or negligible effect on the ability to drive or use machines.

Important information about some of the ingredients of Ondansetron Tablets
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Ondansetron Tablets
Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Swallow each tablet whole with a little water.

Your doctor will decide on the correct dose of ondansetron therapy for you. The dose varies depending on why you are being given ondansetron and on your liver function.

Patients receiving chemotherapy and/or radiotherapy that causes nausea and vomiting:

- **Adults (including the elderly):** The recommended dose is 8 mg 1 to 2 hours before chemotherapy, followed by 8 mg 12 hours later. After the first 24 hours following chemotherapy, ondansetron tablets can be given to prevent nausea and vomiting. The usual dose is 8 mg twice a day, which can be taken up to 5 days.

- **Children aged over 6 months and adolescents (less than 18 years of age):** Ondansetron may be given by injection immediately before chemotherapy, followed by 2 or 4 mg given by mouth twelve hours later (depending on the size of the child). Following this, the dose taken will depend on the size of the child and will be worked out by the doctor. The usual dose is 4 mg or 8 mg three times a day, which may be taken up to 5 days.

To prevent nausea and vomiting after an operation:

- **Adults (including the elderly):** The usual adult dose is 16 mg before the operation, or 8 mg before the operation followed by two further doses of 8 mg at eight hourly intervals.

- **Children aged over 1 month and adolescents (less than 18 years of age):** It is recommended that ondansetron is given as an intravenous injection.

To treat nausea and vomiting after an operation:

- **Adults:** Intravenous administration is recommended.

- **Children aged over 1 month and adolescents:** the doctor will decide the dose. A single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

Patients with moderate or severe liver problems:

- The total daily dose should not be more than 8 mg.

If you notice that the effect of ondansetron is too strong or too weak, talk to your doctor or pharmacist.

If you take more Ondansetron Tablets than you should
If you take too many ondansetron tablets or if someone else has taken some tablets by accident, you should see a doctor at once or go to the hospital emergency department. Take any remaining tablets or the package with you to show the doctor.

If you forget to take Ondansetron Tablets
If you forget a dose and feel sick or vomit, take a tablet as soon as possible and then carry on as before. If you miss a dose but not feel sick take the next dose as on the label.
If you stop taking Ondansetron Tablets
Do not stop taking your tablets, even if you are feeling well, unless your doctor tells you.

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 can cause side effects, although not everybody gets them.

Serious side effects
You should seek medical attention immediately if you experience any of the following:
- Serious allergic reaction which causes swelling of the face or throat, difficulty in breathing or dizziness, or severe itching of the skin with raised lumps.
- Chest pain or irregular heart beat.
- fits (seizures).
- problems with eye movements.
- spasms in the muscles or the head and neck.

Other side effects:
Tell your doctor or pharmacist if any of the following side effects bother you:

Common side effects (affects less than 1 in 10 people) include: headache, constipation, hiccups, feeling flushed or warm.

Uncommon side effects (affects less than 1 in 100 people) include: low blood pressure, slow heart beat, dizziness, increases in liver blood test results.

Rare side effects (affects less than 1 in 1000 people) include: blurred vision, transient blindness...

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

5. How to store Ondansetron Tablets

Keep out of the reach and sight of children.

Do not use Ondansetron Tablets after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.
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 Ondanetron Tablets contain

Ondanetron 4 mg Tablets
The active substance is ondanetron hydrochloride dihydrate. Each film-coated tablet contains ondanetron hydrochloride dihydrate equivalent to 4 mg ondanetron.

Ondanetron 8 mg Tablets
The active substance is ondanetron hydrochloride dihydrate. Each film-coated tablet contains ondanetron hydrochloride dihydrate equivalent to 8 mg ondanetron.

- The other ingredients are:
  core: lactose anhydrous, cellulose microcrystalline, starch (maize) pregelatinised, magnesium stearate.
  coating: hypromellose, lactose monohydrate, titanium dioxide (E171), glycerol triacetate, iron oxide yellow (E172).

What Ondanetron Tablets look like and contents of the pack

Ondanetron 4 mg Tablets are yellow, oval shaped, film-coated tablets, plain on both sides. Ondanetron 8 mg Tablets are yellow, oval shaped, film-coated tablets, plain on both sides.

Ondanetron Tablets are packed in PVC/PVDC//Aluminium blisters.

Pack sizes:
Blisters containing 6, 10, 15, 20, 30, 50 and 100 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Sandoz Ltd
37 Woolmer Way
Bordon
Hampshire
GU35 9QE
United Kingdom

Manufacturer
Saftas Pharma GmbH
Dieselsraße 5
70839 Gerlingen
Germany

Lek Pharmaceuticals d.d.
Verovnikova 57
1526 Ljubljana
Slovenia

Saftas Pharma GmbH
Otto-von-Guericke-Allee 1
39179 Bielefeld
Germany

LEK S.A.
ul. Domaniewaka 50C
02-672 Warsaw
Poland

This leaflet was last approved in 122009 (to be amended after approval)
Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING BOX (FOR BLISTERS)

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg Film-coated Tablets
Ondansetron 8 mg Film-coated Tablets
Ondansetron (as hydrochloride dihydrate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains ondansetron 4 mg (as ondansetron hydrochloride dihydrate).
Each tablet contains ondansetron 8 mg (as ondansetron hydrochloride dihydrate).

3. LIST OF EXCIPIENTS

Also contains: Lactose anhydrous and Lactose monohydrate
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
6 film-coated tablets
10 film-coated tablets
15 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
   EXP

9. SPECIAL STORAGE CONDITIONS
   This medicinal product does not require any special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
   Sandoz Ltd
   Woolmer Way, Bordon, Hants, GU35 9QE, UK.

12. MARKETING AUTHORISATION NUMBER(S)
   PL 04416/0875
   PL 04416/0876

13. MANUFACTURER'S BATCH NUMBER
   Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
   POM

15. INSTRUCTIONS ON USE
   Use as directed by your doctor.

16. INFORMATION IN BRAILLE
   Ondansetron 4 mg Film-coated Tablets
   Ondansetron 8 mg Film-coated Tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (PVC/PVDC/Aluminium)

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg Film-coated Tablets
Ondansetron 8 mg Film-coated Tablets

Ondansetron (as hydrochloride dihydrate)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PL 04416/0875
PL 04416/0876
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING BOX (FOR BLISTERS)

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg Film-coated Tablets
Ondansetron 8 mg Film-coated Tablets
Ondansetron (as hydrochloride dihydrate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains ondansetron 4 mg (as ondansetron hydrochloride dihydrate).
Each tablet contains ondansetron 8 mg (as ondansetron hydrochloride dihydrate)

3. LIST OF EXCIPIENTS

Also contains: Lactose anhydrous and Lactose monohydrate
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
6 film-coated tablets
8 film-coated tablets
10 film-coated tablets
12 film-coated tablets
15 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets
60 film-coated tablets
100 film-coated tablets
5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use

Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sandoz Ltd
Woolmer Way
Bordon
Hants
GU35 9QE
UK

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 04416/0877
PL 04416/0878
<table>
<thead>
<tr>
<th>13. MANUFACTURER'S BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use as directed by your doctor.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron 4 mg Film-coated Tablets</td>
</tr>
<tr>
<td>Ondansetron 8 mg Film-coated Tablets</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>BLISTER (PVC/PVDC//Aluminium)</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Ondansetron 4 mg Film-coated Tablets  
   Ondansetron 8 mg Film-coated Tablets  
   Ondansetron (as hydrochloride dihydrate)

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Sandoz Ltd

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**

   PL 04416/0877  
   PL 04416/0878
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Ondansetron 4mg and 8mg Film-Coated Tablets (PL 04416/0875-8; UK/H/1338-9/001-2/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS) and the following member states as concerned member states (CMS):
   UK/H/1338/001-2/DC – Germany, Ireland, Italy and Luxembourg
   UK/H/1339/001-2/DC – Austria, Germany and Poland

The products are prescription-only medicines for the following:
   Adults:
   Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, Prevention and treatment of post-operative nausea and vomiting (PONV).

   Paediatric Population:

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Zofran 4mg and 8mg Filmtabletten, which were originally granted to GlaxoSmithKline Pharma, Vienna, in May 1991.

Ondansetron hydrochloride is an antiemetic, indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV). It is a potent and highly selective 5HT3 receptor-antagonist which competitively blocks vagal 5-HT3 receptors though the exact mechanism of action is unclear.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 11th December 2009. After a subsequent national phase, the licences were granted in the UK on 12th January 2010.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Ondansetron 4mg Film-Coated Tablets  
| Ondansetron 8mg Film-Coated Tablets |
| Name(s) of the active substance(s) (INN) | Ondansetron hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Alimentary tract and metabolism, antiemetics and antinauseants, serotonin (5HT3) antagonists (A04AA01) |
| Pharmaceutical form and strength(s) | 4mg and 8mg Film-Coated Tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1338-9/001-2/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/1338/001-2/DC – Germany, Ireland, Italy and Luxembourg  
| UK/H/1339/001-2/DC – Austria, Germany and Poland |
| Marketing Authorisation Number(s) | PL 04416/0875-8 |
| Name and address of the authorisation holder | Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE, United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

INN: Ondansetron hydrochloride dihydrate
Chemical Name: (3RS)-9-Methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one hydrochloride dihydrate
Molecular Formula: C_{18}H_{19}N_{3}O \cdot HCl \cdot 2H_{2}O

Appearance: White to off-white powder, sparingly soluble in water and alcohol, soluble in methanol, slightly soluble in methylene chloride.

All aspects of the manufacture and control of the drug substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

P.  Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose anhydrous, cellulose microcrystalline, starch pregelatinised, magnesium stearate, hypromellose, lactose monohydrate, titanium dioxide, triacetin and yellow iron oxide.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of yellow iron oxide (which is controlled to a suitable National Formulary specification). Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

With the exception of lactose anhydrous, none of the excipients are sourced from animal or human origin. Suitable statements have been provided for lactose anhydrous, stating that the lactose is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate film-coated tablets, containing qualitatively and quantitatively the same active substance as Zofran 4mg and 8mg Tablets (GlaxoSmithKline), and exhibiting the same bioavailability in order to comply with the regulations pertaining to abridged applications.

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products. Zofran 8mg Tablets (GlaxoSmithKline, Germany) was used as the
reference product in the bioequivalence study. This is considered to be equivalent to the UK reference product.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
Both strengths of tablets are packaged in polyvinylchloride/aluminium/polyvinylidene chloride blisters in pack sizes of 6, 8, 10, 12, 15, 20, 30, 50, 60 and 100 film-coated tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no specific storage conditions.

Suitable post approval stability commitments have been provided.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron hydrochloride dihydrate are well-known, no further studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Ondansetron 8mg Film-Coated Tablets versus the reference product Zofran 8mg Tablets (GlaxoSmithKline, Germany) in healthy volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 12 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The two treatment arms were separated by a 7 to 14-day washout period.

The log-transformed pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric mean</th>
<th>Confidence limits</th>
<th>Intra-individual CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-tlast (ratio test/reference)</td>
<td>1.04</td>
<td>0.96-1.12</td>
<td>15.34</td>
</tr>
<tr>
<td>Cmax (ratio test/reference)</td>
<td>1.11</td>
<td>1.01-1.22</td>
<td>18.96</td>
</tr>
<tr>
<td>Tmax (h) (difference test-reference)</td>
<td>-0.17</td>
<td>-0.5-0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

The test and reference products are within conventional 90% confidence interval limits for ondansetron hydrochloride. In conclusion, bioequivalence has been shown between the test and reference products.

As the 4mg and 8mg products meet all the criteria as specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the
results and conclusions of the bioequivalence study on the 8mg strength can be extrapolated to the 4mg strength tablets also.

**Efficacy**  
No new data on the efficacy have been submitted and none are required for these types of applications.

**Safety**  
No new or unexpected safety issues were raised by the bioequivalence data.

**SPC, PIL, Labels**  
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

**Clinical Expert Report**  
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**  
The grant of marketing authorisations is recommended.

### IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

#### QUALITY

The important quality characteristics of Ondansetron 4mg and 8mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

#### PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

#### EFFICACY

Bioequivalence has been demonstrated between the applicant’s Ondansetron 8mg Film-Coated Tablets and its respective reference product. As the 8mg and 4mg products meet all the criteria as specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 8mg strength can be extrapolated to the 4mg strength tablets also.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

#### RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with ondansetron hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>