Public Assessment Report

Decentralised

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

UK/H/1136/01/DC
UK/H/1136/02/DC

Aurobindo Pharma Ltd

TABLE OF CONTENTS

Module 1

Product Name	Ondansetron 4mg Film-coated Tablets Ondansetron 8mg Film-coated Tablets
Type of Application	Standard Abriged Decentralised (Article 10.1)
Active Substance (INN)	Ondansetron hydrochloride dihydrate
Pharmacotherapeutic Classification (ATC)	A04AA Serotonin (5HT3) antagonists
Pharmaceuctical Form and Strength	4mg and 8mg Film-coated Tablets
Procedure Numbers	**UK/H/1136/01-02**
RMS	UK
CMS	**AT, BE, DE, ES, FR, HU, IE, IT, NL, NO, PL, SE**
Start Date	15/052007
End Date	16/09/2008
MA Number	PL 20532/1090-10
Name and address of MA holder	Aurobindo Pharma Ltd Ares Odyssey Business Park, West End Road, South Ruislip HA4 6QD, UK

Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate).
Excipients: Each tablet contains 19.137 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, oval shaped, film-coated tablets debossed with 'E' on one side and '01' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron is 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).

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 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: 8 mg 1-2 hours before treatment, followed by 8 mg 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal 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.

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.

Children (aged 2 years and over) and adolescents (< 18 years)

Experience in paediatric patients is limited. In children older than two years, ondansetron may be administered as a single intravenous dose of 5 mg/m^2 over 15 minutes immediately before chemotherapy, followed by 4 mg orally twelve hours later. Oral treatment with a dose according to the body area should be continued for up to 5 days after a course of treatment. Children with a total body area between 0.6 and 1.2 m^2 should receive a dosage schedule of 4 mg 3 times a day, while children with a body area above 1.2 m^2 should receive 8 mg 3 times a day.

There is no experience in children younger than 2 years old.

Ondansetron cannot be used in children with a total body surface below 0.6 m^2.

Elderly

Ondansetron is well tolerated by patients over 65 years and 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 8 mg at eight hourly intervals.

Treatment of established PONV

For the treatment of established PONV intravenous administration is recommended.

Children (aged 2 years and over) and adolescents (< 18 years)

For the prevention and treatment of PONV slow intravenous injection is recommended.

Elderly

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting (PONV) in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.
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 is 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 8 mg should not be exceeded.

4.3 Contraindications

Hypersensitivity to ondansetron or to 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 5-HT3 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.

This product contains 19.137 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ondansetron should not be used in children with a total body surface below 0.6 m^2.
The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.

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 metabolizing 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.

4.6 Pregnancy and lactation

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or fetus, 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 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
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-HT_3- 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.

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during rapid intravenous 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.

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, symptomatic and supportive therapy should be given as appropriate.

The use of ipecacuanha to treat overdose with Ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of Ondansetron itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin ($5\text{-}HT_3$) antagonists
ATC Code: A04AA01

Ondansetron is a potent, highly selective $5\text{-}HT_3$ receptor-antagonist.
Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT3 receptors.

Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

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.

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 140 L. 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.

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 2mg (3-7 years old) or 4mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300mL/min at 12 years of age to 100mL/min at 3 years. Volume of distribution fell from about 75L at 12 years to 17L at 3 years. Use of weight-based dosing (0.1mg/kg up to 4mg 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.

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.

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 with 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

Tablet core:
Lactose anhydrous
Cellulose, microcrystalline
Starch, pregelatinised (maize)
Magnesium stearate

Film coating:
Hypromellose
Triacetin
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/ Aluminium)
Pack size: 4, 6, 7, 10, 14, 15, 28, 30, 49, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed off in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

8 MARKETING AUTHORISATION NUMBER

PL 20532/0109

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/09/2008

10 DATE OF REVISION OF THE TEXT

16/09/2008

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ondansetron 4 mg film-coated tablets
Ondansetron 8 mg film-coated tablets

Ondansetron (as hydrochloride dihydrate)

This medicinal product is known as Ondansetron 4 mg / 8 mg film-coated tablets but will be known as Ondansetron throughout the leaflet.

Read all of this leaflet carefully before you start using 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 IS AND WHAT IT IS USED FOR

This medicine contains ondansetron, which belongs to a group of medicines called anti-emetics.

Ondansetron is used to treat nausea (feeling sick) and vomiting (being sick) caused by some medical treatments, such as chemotherapy or radiotherapy. It is also used to prevent nausea and vomiting in patients following an operation.

2. BEFORE YOU TAKE ONDANSETRON

Do not take Ondansetron
- if you are allergic (hypersensitive) to ondansetron or any of the other ingredients of Ondansetron
- if you have ever had any allergic (hypersensitive) reaction with other anti-emetics (for example granisetron or dolasetron)

Take special care with Ondansetron
- if you have a blockage in your gut or suffer from severe constipation
- if you are due to have surgery to the adenoids or tonsils
- if you have a heart problem
- if you have liver problems

If any of the above apply, you should inform your doctor before beginning treatment with Ondansetron.

Using other medicines
Ondansetron may have an effect on other drugs and other drugs may have an effect on ondansetron.

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription, natural supplements or vitamins or minerals.

In particular it is important to tell your doctor if you are taking, or are about to start treatment with, any of the following medicines as the dose may need to be adjusted:
- Medicines used to treat epilepsy (phenytoin, carbamazepine) - these medicines may reduce the effect of ondansetron
- Antibiotics (rifampicin) - these can reduce the effect of ondansetron
- Medicines used to treat pain (tramadol) - the effect of this medicine may be reduced by ondansetron
- Medicines used to treat heart problems (anti-arrhythmics and/or beta-blockers)

Pregnancy:
It is not recommended that ondansetron be taken during pregnancy. If it is absolutely necessary it should be given with caution especially in the first trimester.

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

Breast-feeding:
If you are taking ondansetron you should not breast-feed your baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ondansetron is unlikely to affect your ability to drive or operate machinery.

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

3. HOW TO TAKE ONDANSETRON

Always take Ondansetron exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Treatment of sickness (nausea and vomiting) in patients receiving chemotherapy or radiotherapy:

Adults (including the elderly): The usual dose is 8 mg of Ondansetron 1 - 2 hours before chemotherapy or radiotherapy, followed by 8 mg of Ondansetron 12 hours later. To protect against delayed, or further, sickness a dose of 8 mg of Ondansetron may be continued twice a day for up to 5 days after treatment.

Children (aged 2 years and over) and adolescents (under 18 years old):
Your doctor will decide what dose of Ondansetron should be given. This will depend on the age and size of the child.

Ondansetron should not be given to children below 2 years or children who are very small.

Prevention of sickness (nausea and vomiting) after an operation:

Adults (including the elderly):

The usual dose is either 16 mg of Ondansetron one hour before the operation or 8 mg of Ondansetron one hour before the operation, followed by two further doses of 8 mg 8 hours apart.

Children (aged 2 years and over) and adolescents (under 18 years old):
The doctor may decide to give an injection rather than tablets.

Patients with liver problems:
The total daily dose should not be more than 8 mg.

If you take more Ondansetron than you should
Do not to exceed the stated dose as doing so could make you ill. If you have taken too many tablets it is important to ask your doctor or pharmacist what to do, or contact your nearest hospital casualty department, without delay. Take these tablets with you.

If an overdose has been taken, symptoms may include problems with vision, low blood pressure (which could cause dizziness or faintness) and palpitations (irregular heart beat).

If you forget to take Ondansetron
If you forget to take a dose, take it as soon as you remember unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop using Ondansetron
Do not stop taking your tablets, even if you are feeling well, without consulting a doctor.

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.

Common side effects: at least 1 of 100 patients treated:
- Headache
- Sensation of flushing and warmth
- Constipation

Uncommon side effects: at least 1 of 1,000 patients treated:
- Involuntary movements of the body, including upward movement of the eyes
- Fits (seizures / convulsions)
- Palpitations (Irregular heartbeat) or slow heart rate
- Chest pain
- Low blood pressure
- Hiccups
- An increase in liver function tests (most often in patients receiving chemotherapy with cisplatin)

Rare side effects: at least 1 of 10,000 patients treated:
- An immediate allergic reaction, which may be serious and include symptoms such as swelling of the mouth, and throat causing difficulty in breathing. **IF THIS SHOULD OCCUR, SEEK URGENT MEDICAL ATTENTION.**
- Visual disturbances e.g. blurred vision (though this has almost always been associated with an ondansetron injection rather than tablets).

Very rare side effects: at least 1 of 10,000 patients treated:
- Temporary loss of vision (however, as with other visual disturbances, such as blurred vision, this has almost always been reported with an ondansetron injection, rather than tablets, and usually with chemotherapy containing cisplatin).

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

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

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

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

6. FURTHER INFORMATION

What Ondansetron contains
The active substance is ondansetron hydrochloride dihydrate.
Each tablet contains 4 mg of ondansetron (as ondansetron hydrochloride dihydrate).
Each tablet contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate).

The other ingredients are

Tablet core:
Lactose anhydrous
Cellulose,microcrystalline
Starch, pregelatinised (maize)
Magnesium stearate

Film coat:
Triacetin
Titanium dioxide
Hypromellose
Iron oxide yellow (for 8 mg tablets only)

What Ondansetron looks like and contents of the pack
Film-coated tablet.

White to off-white, oval shaped, film-coated tablets debossed with 'E' on one side and '01' on the other side.
Yellow, oval shaped, film-coated tablets debossed with 'E' on one side and '02' on the other side.

Ondansetron 4 mg film-coated tablets are available in packs of 4, 6, 7, 10, 14, 15, 28, 30, 49, 50 & 100 tablets.
Ondansetron 8 mg film-coated tablets are available in packs of 4, 5, 6, 10, 15, 30, 49, 50 & 100 tablets.

Not all pack sizes may be marketed.

Also leaflet is available in forms suitable for the partially sighted upon request.

Marketing Authorisation Holder
Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

Manufacturer
Milpharm Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

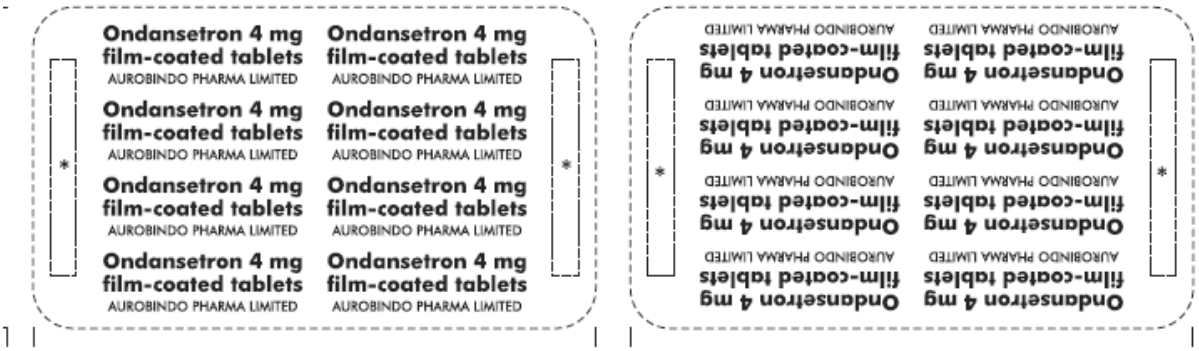
This medicinal product is authorised in the Member States of the EEA under the following names:

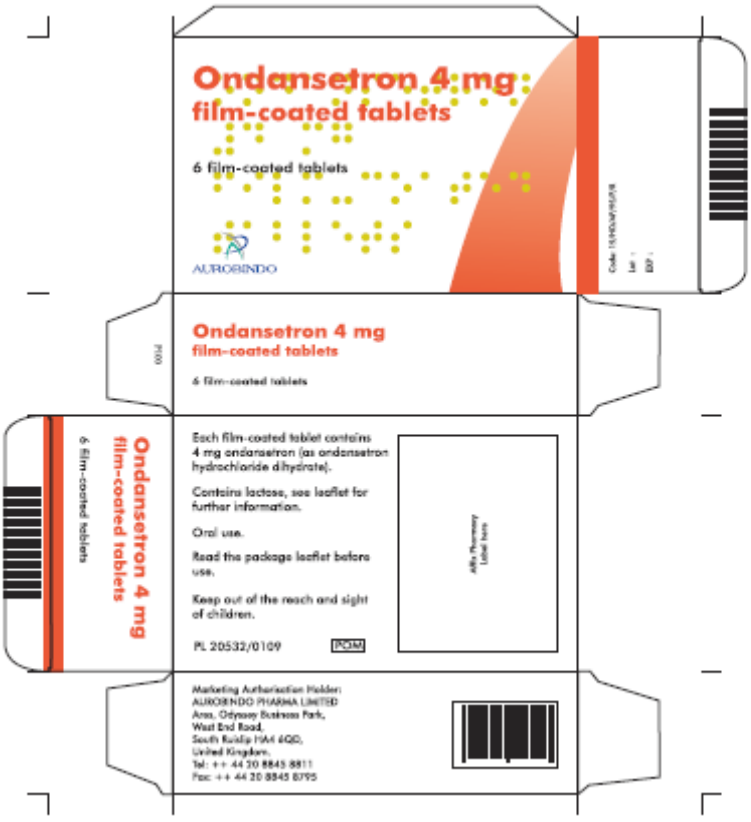
Austria	Ondansetron Aurobindo 4 mg/ 8 mg Filmtabletten
Belgium	Ondansetron Aurobindo 4 mg/ 8 mg, comprimés pelliculés
Germany	Ondansetron Aurobindo 4 mg/ 8 mg Filmtabletten
Hungary	Ondansetron Aurobindo 4 mg/ 8 mg filmtabletta
Ireland	Ondansetron Aurobindo 4 mg/ 8 mg, film-coated tablets
Italy	Ondansetron Aurobindo 4 mg/ 8 mg compresse rivestite con film
Norway	Ondansetron Aurobindo 4 mg/ 8 mg filmdrasjerte tabletter
Poland	Ondansetron Aurobindo 4 mg/ 8 mg
Spain	Ondansetrón Aurobindo 4 mg/ 8 mg comprimidos recubiertos con película
Sweden	Ondansetron Aurobindo 4 mg/ 8 mg, filmdragerade tabletter
The Netherlands	Ondansetron Aurobindo 4 mg/ 8 mg, filmomhulde tabletten
United Kingdom	Ondansetron 4 mg/ 8 mg, film-coated tablets

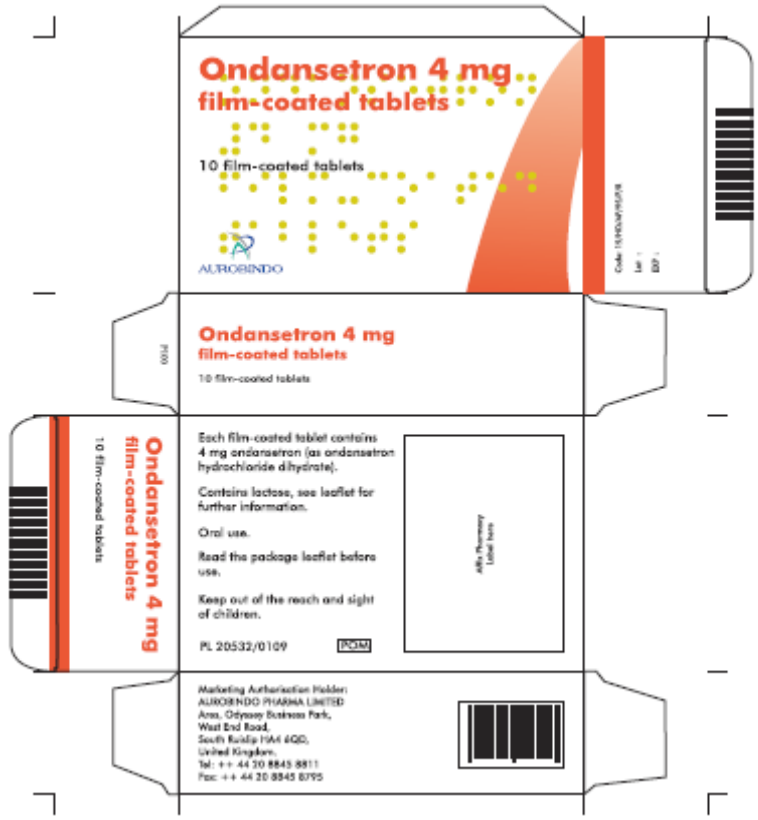
This leaflet was last approved in 08/2008.

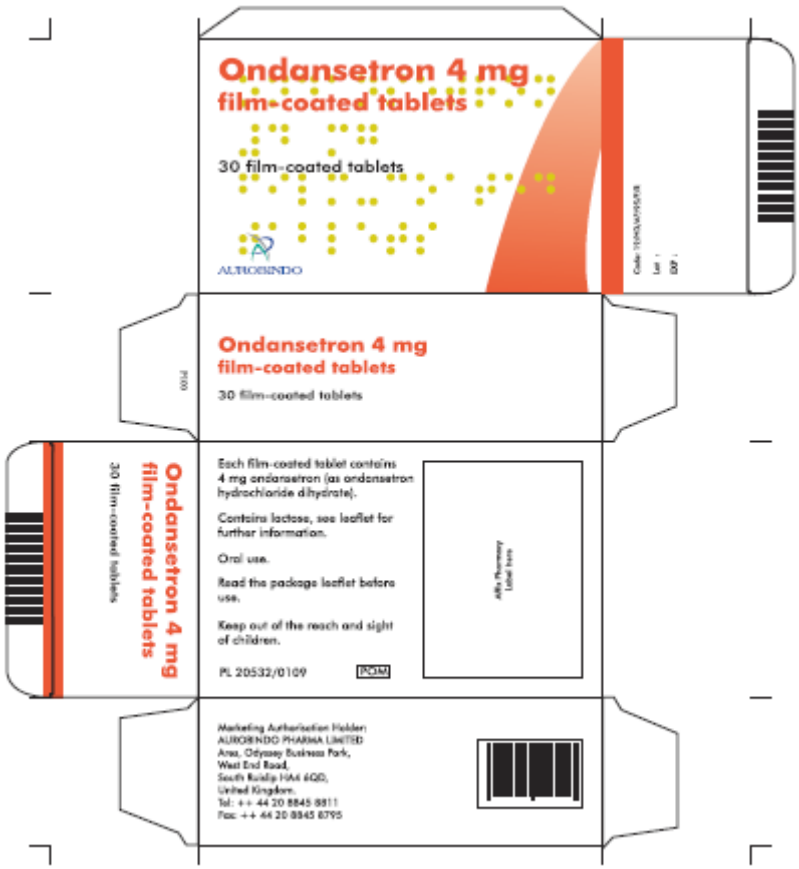
Module 4

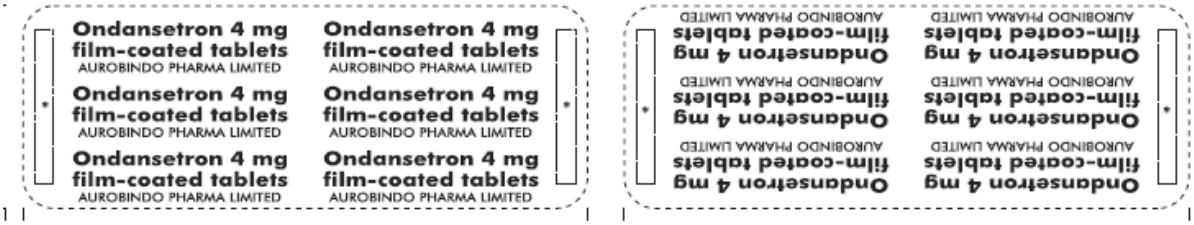
Labelling

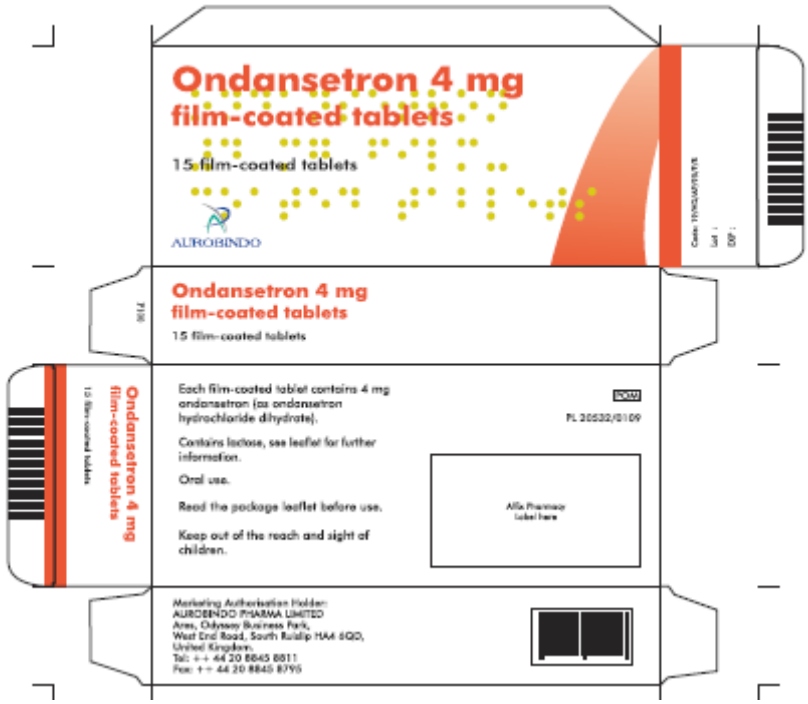





Ondansetron 4 mg
film-coated tablets
10 film-coated tablets
AUROBINDO
Ondansetron 4 mg
film-coated tablets
10 film-coated tablets
Ondansetron 4 mg
film-coated tablets
10 film-coated tablets
Each film-coated tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate).
Contains lactose, see leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
PL 20532/0109
POM
Marketing Authorisation Holder:
AUROBINDO PHARMA LIMITED
Area. Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795


Ondansetron 4 mg
film-coated tablets
30 film-coated tablets
AUROBINDO
Ondansetron 4 mg
film-coated tablets
30 film-coated tablets
Ondansetron 4 mg
film-coated tablets
30 film-coated tablets
Each film-coated tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate).
Contains lactose, see leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
PL 20532/0109
POM
Marketing Authorisation Holder:
AUROBINDO PHARMA LIMITED
Area. Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795


Ondansetron 4 mg
film-coated tablets
AUROBINDO PHARMA LIMITED


Ondansetron 4 mg
film-coated tablets
15 film-coated tablets
AUROBINDO
Ondansetron 4 mg
film-coated tablets
15 film-coated tablets
Each film-coated tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate).
Contains lactose, see leaflet for further information.
Oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
PL 20032/0109
Marketing Authorisation Holder:
AUROBINDO PHARMA LIMITED
Ares, Odyssey Business Park,
West End Road, South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Ondansetron 4mg and 8mg film-coated tablets, for the treatment of nausea and vomiting is approvable.

EXECUTIVE SUMMARY

Problem statement

This is an abridged application made according to Article 10(1) of Directive 2001/83/EC submitted within the Decentralised Procedure with the UK acting as the Reference member State (RMS).

About the product

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 $5HT_3$ receptor-antagonist which competitively blocks vagal 5-HT_3 receptors although the exact mechanism of action is unclear.

General comments on the submitted dossier

The submitted dossier is considered to be adequate in terms of content and format.
No new preclinical studies were submitted with this application.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

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.

The GLP status of literature data cannot be verified, but it is assumed that the studies conducted by the originator would have been in compliance with the standards prevailing at

the time.

The bioequivalence study was conducted according to the principles of GCP.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Ondansetron hydrochloride dihydrate 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 cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on two batches for each tablet strength. The batch analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guidelines. The control tests and specifications for drug product are generally satisfactory, with minor amendments requested.
The proposed shelf-life of 24 months with no storage conditions specified for the drug product was supported by data which met current requirements and was accepted.

Non-clinical aspects

No new preclinical studies were submitted with this application. This is acceptable as ondansetron is a well known active ingredient and no new preclinical issues are considered to arise as a result of its inclusion in the proposed product.

Clinical aspects

A single bioequivalence study was conducted (Study Ods-03/06) comparing, under fasting conditions, the oral bioavailability of the proposed product Ondansetron 8mg film-coated tablets (Test), manufactured by Aurobindo Pharma Ltd, India and Zofran 8mg film-coated tablets (Reference), GlaxoSmithKline, UK. It was conducted according to GCP with an adequate design and based on the study findings both Test and Reference formulations have been shown to be bioequivalent. Although the study was conducted with only one strength these data can be extrapolated to the 4mg film-coated tablet.

Study design

This was an open-label, randomised, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioavailability study of Ondansetron 8mg

film-coated tablets (Test), manufactured by Aurobindo Pharma Ltd, India and Zofran 8mg film-coated tablets (Reference), GlaxoSmithKline, UK. It was conducted in healthy men under fasting conditions. It was conducted between 10th and 20th July 2006. There was a 7 day washout period between doses. It was designed to compare the rate and extent of absorption of ondansetron hydrochloride from the Test and Reference formulations.

The study was conducted according to the principles of GCP.

After an overnight fast (minimum 10h) subjects received a single oral dose according to the randomisation schedule. Serial blood samples for plasma ondansetron assay were taken prior to dosing then at 0.24, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0 and 36.0 hours post dose.

Blood samples were centrifuged under refrigeration as soon as possible after collection and plasma samples were initially stored at <-20ºC then at -70 ºC pending assay.

Standardised meals were provided at 4.35 and 13 hours post-dosing as well as a standardised snack at 8.25hours post-dosing.

Assessor's comment. ***The study design is satisfactory and the washout period adequate.***

Test and reference products

Ondansetron 8mg film-coated tablets by Auribindo Pharma Ltd, India [Test] (batch No, OS0806001; exp. date 05/2008) has been compared to Zofran 8mg film-coated tablets, GlaxoSmithKline) batch No. R182357 from the UK market, exp.date 06/2008 [Reference].

Assessor's comment: the reference product is appropriate.

Population studied

30 (+2 stand-by) healthy adult Indian (Asian race) males with a mean age of 26 years (range 18-41 years) were enrolled as per protocol. In accordance with the stipulated inclusion criteria they had a BMI within the range 19 to 26kg/m^2.

Assessor's comment: an appropriate population was studied.

Pharmacokinetic Variables

Pharmacokinetic analysis was carried-out at the Bioanalytical Unit of APL Clinical Pharmacology Unit, Bachupally Village, Hyderabad, India.

Calculation of pharmacokinetic parameters for ondansetron was performed using drug concentration-time profiles (non-compartmental method).

The following parameters were derived using WinNonlin version 5.0.1.

T_{max}
C_{max}
AUC_{0-t}
$AUC_{0-\infty}$

Assessor's comment: the appropriate variables were measured.

Statistical methods

One subject was withdrawn from the study prior to the second dosing period because of a non drug-related event (malaria). He was replaced and therefore the analysis was conducted with 30 subjects who completed the study.

Statistical analysis was carried-out at the Bioanalytical Unit of APL Clinical Pharmacology Unit, Bachupally Village, Hyderabad, India.

PROC GLM of SAS software release 9.1.3 version was used for statistical analysis. Summary statistics, ANOVA, 90% CIs, Ratio Analysis and intrasubject variability were calculated using SAS 9.1.3 version.

The 90% Confidence Intervals (CIs) were derived for the ratios of the means of log-transformed PK parameters C_{max}, AUC0-t and $AUC_{0-\infty}$ for test and reference formulations. The standard criteria for bioequivalence were applied i.e. CIs within the limits of 80-125%.

Assessor's comment: the statistical methodology is accepted.

Results

Pharmacokinetics

The geometric mean of maximum plasma Ondansetron concentrations (Cmax) for the Test and Reference formulations were 35.67 ng/mL and 37.53 ng/mL respectively.

The average T_{max} for the Test and Reference formulations was 1.88 and 2.00 hours respectively.

The geometric mean of AUCo-t for the Test and Reference formulations were 223.23 hr.ng/mL and 246.34 hr.ng/mL respectively.

The geometric mean of $AUC_{o-\infty}$ for the Test and Reference formulations were 233.73 hr.ng/mL and 259.95 hr.ng/mL respectively.

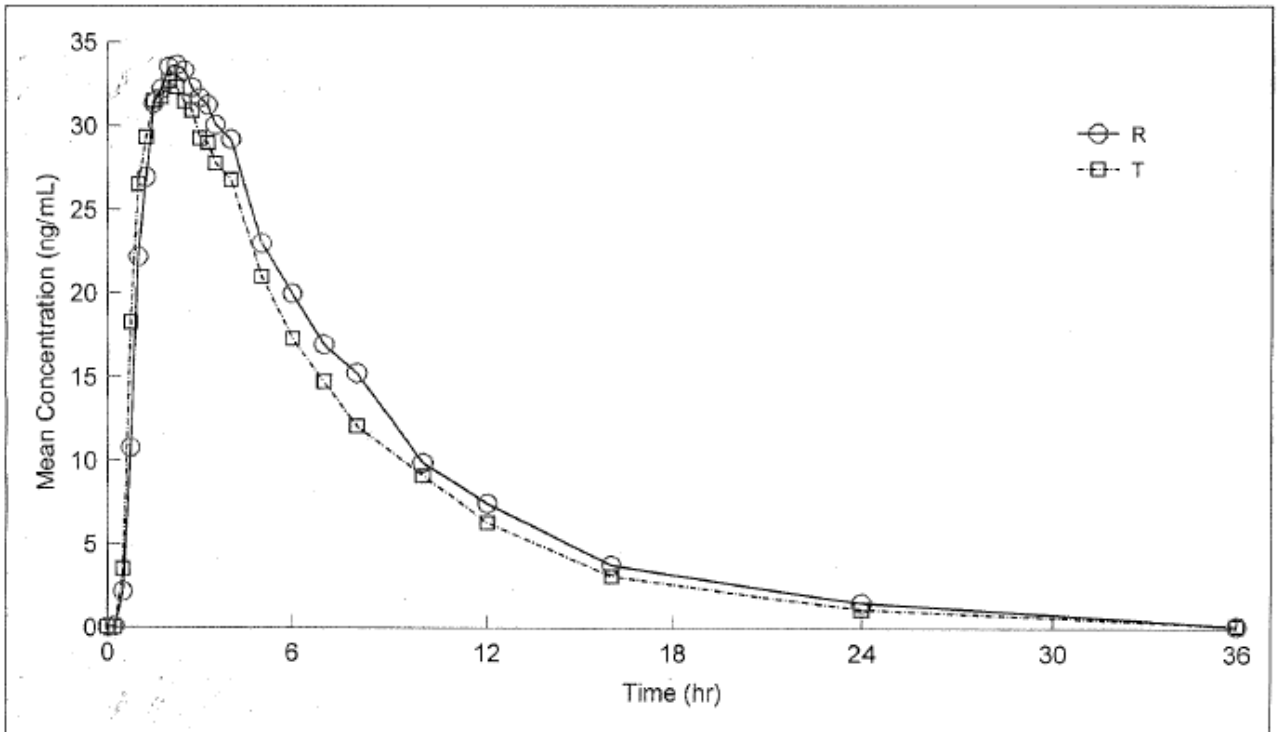
The point estimates for C_{max}, AUC_{o-t}, and $AUC_{o-\infty}$, were 95.06%, 90.62% and 89.91% respectively.

The 90% CI s and Test/Reference (T/R) ratio for the Test formulation - Ondansetron 8mg tablets [Aurobindo Pharma Ltd] to the Reference formulation – 8mg film-coated tablets [GlaxoSmithKline, UK] fell within the standard bioequivalence acceptance range of 80-125%.

The results are summarised in Figures 1 & 2 and in Tables 1 and 2.

Figure 1

Linear Plot Of Mean Plasma Ondansetron Concentrations Versus Time In Healthy, Adult, Male Human Subjects (N=30)



Semi – log Plot of Mean Plasma Ondansetron Concentrations Versus Time in Healthy, Adult, Male, Human Subjects (N=30)

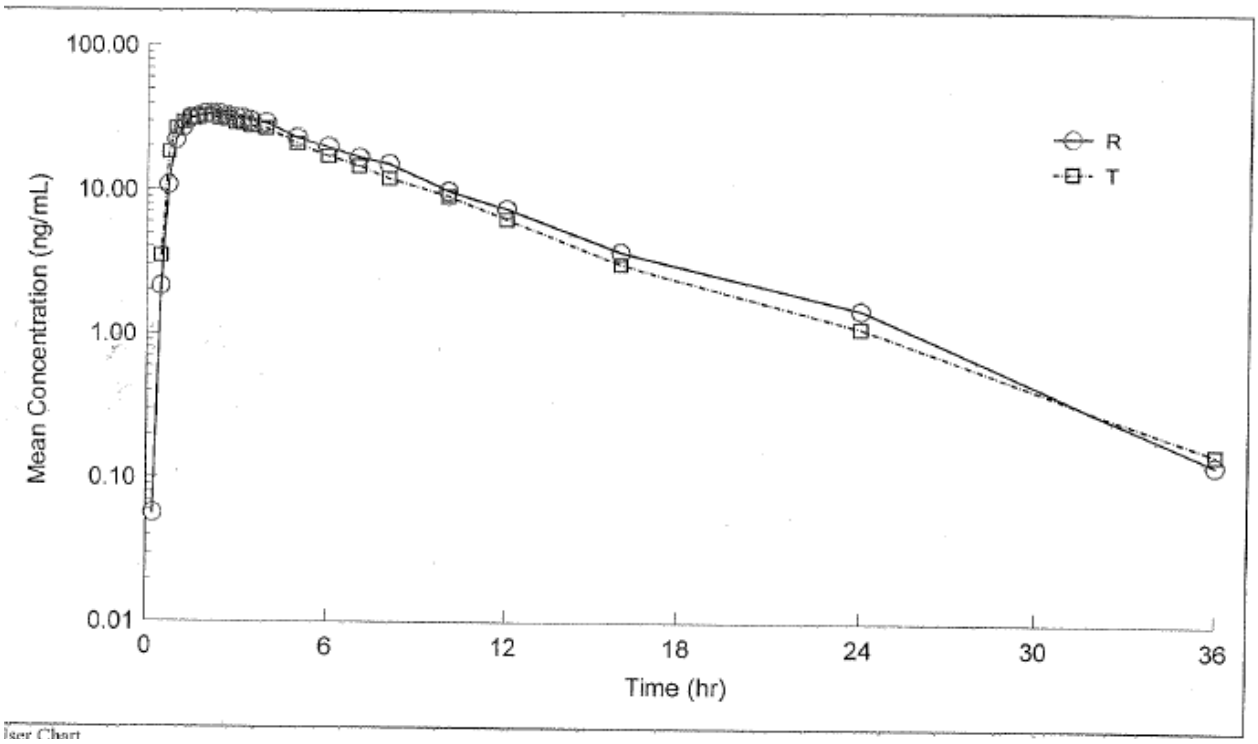


Table 1. Summary Statistics of Pharmacokinetic parameters (non-transformed values)

Statistics		C_{max} (ng/mL)	$AUC_{0\rightarrow t}$ (hr. ng /mL)	$AUC_{0\rightarrow \infty}$ (hr. ng /mL)	T_{max} (hr)*
Test Formulation	N	30	30	30	30
	Mean	37.66	243.44	253.95	1.88
	S.D.	12.720	110.952	113.893	0.748
	C.V. (%)	33.78	45.58	44.85	38.51
Reference Formulation	N	30	30	30	30
	Mean	39.21	266.19	280.47	2.00
	S.D.	11.185	102.192	107.470	1.465
	C.V. (%)	28.53	38.39	38.32	61.67

* For T_{max} instead of mean, median has been used

Table 2. Log-transformed data with ratios and 90% CIs

Parameters	Lntransformed Data					
	Geometric Mean		(T/R) Ratio (%)	90% Confidence Interval (%)	Intra Subject CV (%)	Power (%)
	Test	Reference				
C_{max}	35.67	37.53	95.06	89.01 - 101.52	15.05	100
$AUC_{0\rightarrow t}$	223.23	246.34	90.62	86.24 - 95.22	11.31	100
$AUC_{0\rightarrow \infty}$	233.73	259.95	89.91	85.54 - 94.51	11.38	100

The results demonstrate bioequivalence of the test product to the reference product.

Pharmacodynamics
No new studies have been performed and none is required for this type of application.

Clinical efficacy
No new studies have been performed and none is required for this type of application.

Clinical safety
The bioequivalence study has raised no new safety concerns. The Applicant has stated that a Risk Management Plan (RMP) is not normally required for generic products unless there are safety issues with the reference product. Aurobindo has reviewed the literature and has not identified any ongoing/emerging safety issues with ondansetron and a risk management Plan has therefore not been submitted with this application. The safety profile for the reference product, Zofran, will be used as a basis for risk management. Aurobindo Pharma Ltd, UK, has designed a Pharmacovigilance System and stated that any new signals or possible changes to the benefit-risk balance will be communicated to the Regulatory Authorities.

BENEFIT RISK ASSESSMENT

Given the demonstration of bioequivalence between the proposed product and Zofran the benefit risk can be considered the same as that of the originator product.

Module 6

Steps taken after procedure

No non-confidential changes have been made to the Marketing Authorisation.