IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1236/001/001
Case No: 2059539

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

RMR Pharmaceuticals Limited

Unit 5, Faraday Court, **First Avenue, Centrum 100**, **Burton-upon-Trent**, **Staffs DE14 2WX**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ondansetron 4mg/5ml Oral Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/05/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 4 mg ondansetron, as ondansetron hydrochloride dihydrate.

Excipient: 600 mg of Sorbitol Liquid (E420) per 1ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Colourless to slightly yellow, clear solution with a characteristic smell of strawberry.

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 of post-operative nausea and vomiting (PONV).

4.2 Posology and method of administration

Oral use.

4.2.1. 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 and selected as shown below.

Emetogenic chemotherapy and radiotherapy:

For patients receiving emetogenic chemotherapy or radiotherapy Ondansetron can be given either by oral or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron should initially be administered intravenously 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 treatment with Ondansetron may 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 may 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 above) 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 min. 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 4 mg tablets (nor Ondansetron 8 mg tablets) 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 4.2.3 “Special populations”.

4.2.2. Post-operative nausea and vomiting (PONV)

Prevention of 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 above) 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 4.2.3 “Special populations”.

4.2.3. 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 8 mg 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 *is* required.

4.3 Contraindications

Hypersensitivity to Ondansetron or to other selective 5-HT_3-receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients.

4.4 Special warnings and precautions for use

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

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.

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

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of ondansetron on other medicinal products:
There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol, alfentanil, propofol and thiopental.

Tramadol: Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

Effects of other medicinal products on ondansetron:
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.

4.6 Pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of ondansetron on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women especially in the first trimenon. A careful risk/benefit assessment should be performed.

Lactation
Tests have shown that ondansetron passes into the milk of lactating animals (se 5.3 Preclinical Safety data). 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.

4.8 Undesirable effects

SYSTEM ORGAN CLASS	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to ≤1/100)	Rare (≥1/10,000 to <1/1,000)
Immune system disorders			Immediate hypersensitivity reactions, sometimes severe including anaphylaxis.
Nervous system disorders			Involuntary movement disorders such as extrapyramidal reactions, e.g. oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures.
Cardiac disorders			Chest pain with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia.
Gastrointestinal disorders	Increase of the large bowel transit time and constipation		
Hepato-biliary disorders		Occasional asymptomatic increases in liver function tests	
General disorders and administration site conditions	Headache, sensations of flushing or warmth, hiccups.		

Immune system disorders

Rare: Anaphylaxis may be fatal. Hypersensitivity reactions. were also observed in patients, which were sensible towards other selective 5-HT_3-antagonists.

Nervous system disorders

Rare: Seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects.

Gastrointestinal disorders

Common: Constipation may be caused in some patients. Patients with signs of subacute obstruction should be monitored.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04AA01

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist.

Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$ 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

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.

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.

Ondansetron is not highly protein bound (70-76%). A direct correlation 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 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Studies in healthy elderly volunteers have shown slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).

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 safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.
Ondansetron and its metabolites accumulate in the milk of rats; milk/plasma-ration was 5.2. Ondansetron in submicromolar concentrations blocked cloned hERG potassium channels of the human heart. The clinical relevance of this finding is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Sodium citrate dihydrate
Sodium benzoate (E211).
Sorbitol Liquid (non crystallising)
Strawberry flavour (Propylene glycol E1520, Ethyl alcohol, Water, Benzyl alcohol)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Unopened: 3 years.
Once opened: 6 days

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

One carton containing a 70 ml amber glass bottle, with a child resistant (aluminium) cap, with sealing disc (EPE) and a measuring spoon (LDPE) with graduation 5, 10 and 15ml, containing 50 ml of Ondansetron Syrup.

Pack sizes:
50 ml

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

RMR Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER

PA 1236/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th May 2006

Date of last renewal: 28th May 2009

10 DATE OF REVISION OF THE TEXT

November 2009