IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1236/001/002
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 2mg/ml solution for injection and infusion

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

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml solution for injection and infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 2.494 mg ondansetron hydrochloride dihydrate equivalent to 2 mg of ondansetron.
One 2 ml ampoule contains 4 mg of ondansetron and one 4 ml ampoule contains 8 mg of ondansetron.

Excipient: 2,51 mmol of sodium (57,67 mg) per maximum daily dose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion

A clear solution.

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

For intravenous injection or after dilution for intravenous infusion.
For instructions on dilution of the product before administration, see section 6.6.

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
For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by intravenous or oral administration.
For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron 8 mg should be administered as a slow intravenous injection or as a short-time intravenous infusion over 15 minutes immediately before treatment, followed by 8 mg orally twelve hourly.
To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal 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 or 16 mg rectally once daily.
For oral or rectal administration refer to the SPC of ondansetron tablets and suppositories, respectively.

Highly emetogenic chemotherapy
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, Ondansetron can be given by

intravenous administration.
Ondansetron has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8 mg by slow intravenous injection immediately before chemotherapy.

- A dose of 8 mg by slow intravenous injection or as a short-time intravenous infusion over 15 minutes immediately before chemotherapy, followed by two further intravenous doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

- A single dose of 32 mg diluted in 50-100 ml of sodium chloride 9 mg/ml (0.9 % w/v) solution or other compatible infusion fluid (see compatibility with solutions for infusion under section 6.6) and infused over not less than 15 minutes immediately before chemotherapy.

Doses of greater than 8 mg and up to 32 mg of ondansetron may only be given by intravenous infusion over not less than 15 minutes.
The selection of dose regimen should be determined by the severity of the emetogenic challenge.

The efficacy of Ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of an intravenous dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy.

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. Refer to the SmPC for Ondansetron Tablets 4 mg and 8 mg.
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 2-3 times a day, while children with a body area above 1.2 m^2 should receive 8 mg 2-3 times a day.

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

Elderly:
Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration is required.
See also section 4.2. “Special populations”.

Post-operative nausea and vomiting (PONV)
Prevention of PONV
Adults:
For the prevention of PONV Ondansetron can be administered orally or by intravenous injection.

Ondansetron may be administered as a single dose of 4 mg given by slow intravenous injection at induction of anaesthesia.

Children (aged 2 years and above) and adolescents (< 18 years):
For the prevention of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For oral administration refer to the SPC of ondansetron tablets.

Treatment of establised PONV
Adults: For the treatment of established PONV a single dose of 4 mg given by slow intravenous injection is recommended.

Children (aged 2 years and over) and adolescents (<18 years) :
For treatment of established PONV in paediatric patients, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

There is limited data on the use of Ondansetron in the prevention and treatment of PONV in children below 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 (PONV) in the elderly; however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

See also section 4.2. “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.

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

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

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

The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.

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.

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 4 mg/2 ml solution for injection / Ondansetron 8 mg/4 ml solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium- free'.

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 metabolized 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 (see section 5.3). However animal studies are not always predictive of human response. 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 (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 2 mg/ml has no or negligible influence on the ability to drive and use machines.

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)	Very rare (<1/10,000)
Immune system disorders	-	-	Immediate hypersensitivity reactions, sometimes severe including anaphylaxis. -	-
	-	-	Involuntary	-

Nervous system disorders			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.	Transitory changes in the electrocardiogram, including prolongation of the QT interval.
Gastrointestinal disorders	Increase of the large bowel transit time and constipation in some patients.	-		-
Hepato-biliary disorders		Asymptomatic increases in liver function tests.		-
Skin and subcutaneous tissue disorders		Hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching), sometimes extending along the drug administration vein.		-
General disorders and administration site conditions	Headache, sensations of flushing or warmth, hiccups.		Transient visual disturbances (e.g. blurred vision) and dizziness during rapid intravenous administration of ondansetron. Transitory blindness.	-

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.

Cardiac disorders
Rare: Chest pain and cardiac arrhythmias may be fatal in individual cases.

Very rare: Transitory changes in the electrocardiogram, including prolongation of the QT interval have been observed predominantly after intravenous application of ondansetron.

Hepato-biliary disorders

Uncommon: Reactions of asymptomatic increases in liver function tests, were frequently observed in patients under chemotherapy with cisplatin.

General disorders and administration site conditions

Rare: In individual cases transitory blindness was reported in patients receiving chemotherapeutic agents included cisplatin. Most of reported cases were resolved in 20 minutes.

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

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.
A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption
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 about30 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.
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.

Distribution
The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a 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%).

Metabolism
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Excretion
Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half life is about 3 hours.

Special groups
Children
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.

Elderly persons
Studies in healthy elderly volunteers have shown slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).
Renal impairment
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 (5.4 h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Hepatic impairment
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.

Gender differences
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).

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.
A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride.
Citric acid monohydrate
Sodium citrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those specified in section 6.6.

6.3 Shelf Life

Unopened: 3 years.

Once opened:
Injection:
The product should be used immediately.

Infusion:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8^{o}C .
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

One carton box containing a brown glass ampoule (type I). Dose volumes of 2ml are presented in 2ml ampoules.
One carton box containing a brown glass ampoule (type I). Dose volumes of 4ml are presented in 5ml ampoules.

Pack sizes:
1x2 ml, 5x2 ml, 1x4 ml, 5x4 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Injection:

Solution for injection is for single use only. Any content should be discarded.

Solution for infusion*:*

Can be diluted with solutions for infusion containing: 0.9% sodium chloride, 5% glucose, 10% mannitol, 0.3% potassium chloride+0.9% sodium chloride and 0.3% potassium chloride + 5% glucose as well as with Ringer solution for infusion.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA 1236/1/2

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