IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0126/142/001
Case No: 2006041

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

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Ondansetron 2 Mg/Ml. Solution for Injection

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 **06/07/2007** until **05/07/2012**.

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 2 mg of ondansetron.

1 ampoule with 2 ml solution for injection contains 4 mg ondansetron.
1 ampoule with 4 ml solution for injection contains 8 mg ondansetron.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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.

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 explained 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, 8 mg of ondansetron 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 every twelve hours.
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 of orally administered ondansetron is 8 mg twice daily. For oral treatment, other medicinal products on the market must be used.

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 2 - 4 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%) solution for injection or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes immediately before chemotherapy.

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 a single intravenous dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy. (see section 6.6)
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 of orally administered ondansetron is 8 mg twice daily. For oral treatment, other medicinal products on the market must be used.

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/m2 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 times a day, while children with a body area above 1.2 m^2 should receive 8 mg 2 times a day.

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

Elderly patients
No alteration of dosage, dosing frequency or route of administration is required.

Please also refer to “Special populations”.

Post-operative nausea and vomiting (PONV)
Adults
For the prevention of PONV ondansetron may be administered orally or by intravenous injection.
Ondansetron may be administered as a single dose of 4 mg given by or slow intravenous injection at induction of anaesthesia.
For the treatment of established PONV a single dose of 4 mg given by slow intravenous injection is recommended.

Children (aged 2 years and above) and adolescents (< 18 years)
For 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 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 under 2 years of age.

Elderly patients
There is limited experience in the use of ondansetron in the prevention and treatment of PONV in the elderly.

Please also refer 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.

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 medicinal product 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 the active substance 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 subacute intestinal obstruction should be monitored following administration.

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.

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.

Ondansetron Synthon 2 mg/ml solution for injection contains sodium. The solutions for injection (ampoules with 2 ml and 4 ml ondansetron) contain less than 1 mmol sodium (23 mg) each, i.e. essentially ”sodium-free”.

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, temazepan, 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.

4.6 Pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no undesirable effects of ondansetron on pregnancy or on the health of the foetus/newborn infant. 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. 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 has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Immune system disorders
Rare (> 1/10,000, < 1/1,000): immediate hypersensitivity reactions, sometimes severe, including anaphylaxis. Anaphylaxis may be fatal.

Hypersensitivity reactions were also observed in patients, which were sensitive to other selective 5-HT_3 antagonists.

Nervous system disorders
Rare (> 1/10000, < 1/1000): there have been reports suggestive of involuntary movement disorders such as extrapyramidal reactions e.g. oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae and seizures have been rarely observed although no known pharmacological mechanism can account for ondansetron causing these effects.

Cardiac disorders
Rare (> 1/10000, < 1/1000): chest pain, with or without ST segment depression, cardiac arrhythmias, hypotension and bradycardia.
Gastrointestinal disorders
Common (> 1/100, < 1/10): ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepato-biliary disorders
Occasional asymptomatic increases in liver function tests were observed.

Skin and subcutaneous tissue disorders
Occasionally, hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the medicinal product administration vein.

General disorders and administration site conditions
Common (> 1/100, < 1/10): headache, sensation of flushing and warmth, hiccups.

Rare (> 1/10000, < 1/1000): transient visual disturbances (e.g. blurred vision) and dizziness during rapid intravenous administration of ondansetron.

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 ($5\text{-}HT_3$) 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 $5\text{-}HT_3$ 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 $5\text{-}HT_3$ 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.

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, 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 140L. 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.

Ondansetron is not highly protein bound (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 (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.
Following oral or intravenous 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

5.3 Preclinical safety data

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

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio 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 uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate dihydrate
Sodium chloride
Hydrochloric acid 1M
Hydrochloric acid solution 20% (v/v)
Sodium hydroxide solution 20% (m/v)
Water for injections

6.2 Incompatibilities

Ondansetron solution for injection should not be given in the same syringe or in the same infusion with other medicinal product.

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

6.3 Shelf Life

Unopened: 2 years.

Injection
The medicinal product should be used immediately after opening.

Infusion
Chemical and physical in-use stability has been demonstrated for 7 days at 4 ºC and 25 ºC a concentration ranging from 16 µg/ml up to 640 µg/ml after dilution with the infusion solutions mentioned in section 6.6.

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 ºC, unless reconstitution / dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the ampoule in the outer carton.

6.5 Nature and contents of container

Clear colourless one-point-cut (OPC) glass ampoule (Type I) with a coloured dot.

Package of 5 x 2 ml and 5 x 4 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The medicinal product is for single use only. Any unused solution should be discarded.

The ondansetron solution for injection is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.
Ondansetron solution for injection should only be administered with the following infusion solutions:
- Sodium chloride 0.9 % w/v
- Glucose 5% w/v
- Mannitol 10 % w/v
- Ringer infusion
- Potassium chloride/Sodium chloride 0.3 % / 0.9 % w/v
- Glucose/Potassium chloride 5% / 0.3 % w/v

The use of both PVC infusion bags and Type I glass bottles are considered suitable for dissolution purposes. According to the current knowledge polyethylene infusion bags may also be used for dissolution purposes.

Dilutions of ondansetron solution for injection in sodium chloride 0.9% w/v or in glucose 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that ondansetron solution for injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
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8 MARKETING AUTHORISATION NUMBER

PA 126/142/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th July 2007

10 DATE OF REVISION OF THE TEXT