

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: contains 163.75mg lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval shaped with an embossment 'O' on one side and '8' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ondansetron tablets are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron tablets are also indicated for the prevention of post-operative nausea and vomiting.

4.2 Posology and method of administration

Ondansetron is also available for parenteral use to allow the route of administration and dosing to be flexible.

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.

Emetogenic Chemotherapy and Radiotherapy:-

The recommended oral dose is 8mg 1-2 hours before treatment, followed by 8mg orally 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Ondansetron should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8mg to be taken twice daily.

Highly Emetogenic Chemotherapy:-

Ondansetron can be given by oral, intravenous, or intramuscular administration. The recommended oral dose is 24 mg taken together with oral dexamethasone sodium phosphate 12mg, 1-2 hours before treatment.

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 oral dose is 8mg to be taken twice daily.

Children and Adolescents (aged 6 months to 17 years):-

In children with a body surface area of less than 0.6m^2 an initial i.v. dose of $5\text{mg}/\text{m}^2$ is administered immediately before chemotherapy, followed by a 2mg oral dose 12 hours later. 2mg orally twice daily can be continued for up to five days after a course of treatment.

In children with a body surface area of 0.6 to 1.2m² Ondansetron is administered as a single i.v. dose of 5mg/m² immediately before chemotherapy, followed by a 4mg orally 12 hours later. 4mg Ondansetron, orally twice daily can be continued for up to five days after a course of treatment.

For children with a body surface area of greater than 1.2m² an initial i.v. dose of 8mg is administered immediately before chemotherapy, followed by 8mg orally 12 hours later. 8mg Ondansetron, orally twice daily can be continued for up to five days after a course of treatment.

Alternatively, in children aged 6 months or older, Ondansetron is administered as a single i.v. dose of 0.15mg/kg (not to exceed 8mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of three doses, 4mg orally twice daily can be continued for up to five days after a course of treatment. Adult doses must not be exceeded.

Elderly:-

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

POST-OPERATIVE NAUSEA AND VOMITING

Adults:-

For prevention of post-operative nausea and vomiting the recommended oral dose is 16mg given one hour prior to anaesthesia. For treatment of established post-operative nausea and vomiting Ondansetron administered by injection is recommended.

Children and Adolescents (aged 1 month to 17 years):-

No studies have been conducted on the use of orally administered Ondansetron in the prevention and treatment of post-operative nausea and vomiting, slow intravenous injection is recommended for this purpose.

Elderly:-

There is limited experience in the use of Ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

PATIENTS WITH RENAL IMPAIRMENT

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

PATIENTS WITH HEPATIC IMPAIRMENT

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

PATIENTS WITH POOR SPARTEINE/DEBRISOQUINE METABOLISM:

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

4.3 Contraindications

History of hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃

receptor antagonists.

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 or family history of prolonged QT syndrome.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, frusemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P450 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 Fertility, pregnancy and lactation

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 foetus, 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.

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($< 1/10,000$) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of Ondansetron according to indication and formulation.

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

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

Rare: Dizziness during rapid i.v. administration.

Eye disorders

Rare: Transient visual disturbances (eg. 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: Constipation. Local burning sensation following insertion of suppositories.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests[#].

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

General disorders and administration site conditions

Common: Local i.v. injection site reactions.

4.9 Overdose

There is limited experience of ondansetron overdose. 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 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: antimetics and antinauseants serotonin (5HT₃) antagonists. ATC Code: A04A A01.

Ondansetron is a potent, highly selective 5HT₃ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known.

Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT₃ receptors. Ondansetron blocks the initiation of this reflex.

Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT₃ receptors on neurons located both in the peripheral and central nervous system.

The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing. For doses above 8mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.

Bioavailability is slightly enhanced by the presence of food but unaffected by antacids. The disposition of ondansetron following oral, intramuscular or intravenous dosing is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 h) 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).

In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to undergoing surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months but comparable to the patients aged 3 to 12 years. The half-life in the 1 to 4 month patient population was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. No dose adjustment is necessary for patients aged 1 to 4 months as only a single i.v. dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting. The differences in pharmacokinetic parameters can be explained in part by the higher volume of distribution in the 1 to 4 month patient population.

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 in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were normalised by body weight, the values for these parameters were similar between the different age group populations. 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.

Population pharmacokinetic analysis was performed on 74 patients aged 6 to 48 months following administration of 0.15 mg/kg i.v. ondansetron every 4 hours for three doses for the treatment of chemotherapy induced nausea and vomiting and 41 surgery patients aged 1 to 24 months following administration of a single 0.1 mg/kg or 0.2 mg/kg i.v. dose of ondansetron. Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months,

administration of a 0.15 mg/kg i.v. dose of ondansetron every 4 hours for 3 doses would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery subjects aged 5 to 24 months and previous paediatric studies in cancer (aged 4 to 18 years) and surgical (aged 3 to 12 years) subjects, at similar doses.

In patients with moderate renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced, 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. In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced resulting in prolonged elimination half-lives (15 - 32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

5.3 Preclinical safety data

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose monohydrate
Microcrystalline cellulose
Pregelatinised maize starch
Magnesium stearate

Film Coating

Hypromellose
Titanium dioxide (E171)
Ferric oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ondansetron tablets are packed in PVC/aluminium blisters and are available in packs containing 10 or 30 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd.
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 711/86/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd September 2005

Date of last renewal: 2nd September 2010

10 DATE OF REVISION OF THE TEXT

February 2011