Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection or Infusion (2ml Ampoule)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

A clear, colourless solution, practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ondansetron solution for injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

4.2 Posology and method of adminstration

Ondansetron is also available for oral 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.

The dose range of Ondansetron solution for injection is 8 to 32 mg a day and selected as shown below:-

Emetogenic Chemotherapy and Radiotherapy:-
The recommended intravenous or intramuscular dose of Ondansetron is 8mg administered as a slow injection immediately before treatment.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Highly Emetogenic Chemotherapy:-
For patients receiving highly emetogenic chemotherapy, e.g. High-dose cisplatin. Ondansetron may be administered as a single 8 mg intravenous or intramuscular dose immediately before chemotherapy. Doses of greater than 8 mg and up to 32 mg of Ondansetron may only be given by intravenous infusion diluted in 50-100 ml of saline or other compatible infusion fluid (see *Pharmaceutical Precautions*) and infused over not less that 15 minutes.

Alternatively a dose of 8 mg of Ondansetron may be administered by slow intravenous or intramuscular injection

immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

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.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Children:-
Ondansetron may be administered as a single intravenous dose of 5 mg/m^2 immediately before chemotherapy, followed by an oral dose twelve hours later. Oral therapy should be continued for up to 5 days after a course of treatment.

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

POST-OPERATIVE NAUSEA AND VOMITING

Adults:-
For prevention of post-operative nausea and vomiting the recommended dose of Ondansetron solution for injection is a single dose of 4 mg of intramuscular or slow intravenous injection administered at the induction of anaesthesia.

For treatment of established post-operative nausea and vomiting a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Children:-
For prevention of post-operative nausea and vomiting 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 the treatment of established post-operative nausea and vomiting 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.

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 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 are required.

4.3 Contraindications

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 $5HT_3$ receptor antagonists.

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

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 rifamicin), 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

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

The following side effects can occur: headache, a sensation of warmth or flushing, hiccups and occasional, asymptomatic increases in liver function tests have been reported.

Ondansetron is known to increase large bowel transit time and may cause constipation in some patients. There have been rare reports of immediate hypersensitivity reactions sometimes severe including anaphylaxis. Appropriate supportive therapy should be available. Rare cases of transient visual disturbances (e.g. blurred vision) and dizziness have been reported during rapid intravenous administration of ondansetron. Occasionally local reaction on the site of intravenous injection has been reported.

There have been rare reports suggestive of extrapyramidal reactions such as oculogyric crisis/dystonic reactions without definitive evidence of persistent clinical sequelae.

Seizures have been rarely observed. There have been rare reports of chest pain with or without ST segment depression, arrhythmias, hypotension and bradycardia.

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

Ondansetron is a potent, highly selective $5HT_3$ 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 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

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. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. 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 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 and half-life 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 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 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 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 pharmacokinetics to be essentially unchanged. In patients with severe hepatic impairment, ondansetron 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

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

Sodium chloride
Citric acid monohydrate
Sodium citrate dihydrate
Water for injections

6.2 Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication (see Section 6.6 Instructions for *Use and Handling*).

Ondansetron injection should only be admixed with those infusion solutions which are recommended (see Section 6.6 Instructions for Use and Handling).

6.3 Shelf Life

Unopened: 3 years.

Injection:
The product should be used immediately after opening.

Infusion:
Chemical and physical in-use stability has been demonstrated for 28 days. 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°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the ampoules in the outer carton. Do not refrigerate or freeze.

6.5 Nature and contents of container

Ondansetron solution for injection is filled in clear 2ml glass ampoules, type 1 and is available in a pack size of 5 ampoules.

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

Injection:

For single use. Any unused solution should be discarded.

Infusion:

Compatibility with intravenous fluids:-
Ondansetron solution for injection should only be admixed with those infusion solutions which are recommended.

Sodium Chloride Intravenous Infusion BP 0.9% w/v
Glucose Intravenous Infusion BP 5% w/v
Mannitol Intravenous Infusion BP 10% w/v
Ringers Intravenous Infusion

Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP.
Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type I glass bottles.

Dilutions of Ondansetron 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.

Compatibility with other drugs: -
Ondansetron may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or syringe pump.

The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160micrograms/ml (e.g. 8mg/500ml and 8mg/50ml respectively);

Cisplatin
Concentrations up to 0.48mg/ml (eg.240mg in 500ml) administered over one to eight hours.

5-fluorouracil
Concentrations up to 0.8mg/ml (e.g. 2.4g in 3 litres or 400mg in 500ml) administered at a rate of at least 20ml per hour (500ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin
Concentrations in the range 0.18mg/ml to 9.9mg/ml (eg. 90mg in 500ml to 990mg in 100ml), administered over ten minutes to one hour.

Etoposide
Concentrations in the range 0.144mg/ml to 0.25mg/ml (eg.72mg in 500ml to 250mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime
Doses in the range 250mg to 2000mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5ml for 250mg and 10ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide
Doses in the range 100mg to 1g, reconstituted with Water for Injections BP, 5ml per 100mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin
Doses in the range 10-100mg reconstituted with Water for Injections BP, 5ml per 10mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Dexamethasone
Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous Injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 32mg of ondansetron diluted in 50-100ml of the following infusion fluids:
Sodium Chloride Intravenous Infusion BP 0.9% w/v
Glucose Intravenous Infusion BP 5% w/v
Sodium Chloride Intravenous Infusion 0.9% w/v and Glucose Intravenous Infusion BP 5% w/v over approximately 15 minutes.
Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram - 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for ondansetron.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Ltd.
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 74/54/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 October 2005