Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zofran Zydis 8mg Oral Lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oral lyophilisate contains 8mg ondansetron.

Excipients: Aspartame
Sodium methyl hydroxybenzoate
Sodium propyl hydroxybenzoate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral lyophilisate.

Product imported from Spain and the Netherlands.
White round oral lyophilisate.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zofran Zydis is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Zofran Zydis is also indicated for the prevention of post-operative nausea and vomiting.

4.2 Posology and method of administration

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

Place the Zofran Zydis on top of the tongue, where it will disperse within seconds, then swallow.

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 Zofran should be continued for up to 5 days and rectal treatment for up to 3 days, after a course of treatment. The recommended oral dose is 8mg to be taken twice daily.

Highly Emetogenic Chemotherapy:-
Zofran can be given by oral, intravenous, intramuscular or rectal 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 Zofran should be continued for up to 5 days and rectal treatment for up to 3 days, after a course of treatment. The recommended oral dose is 8mg to be taken twice daily.

Children:-
In children Zofran is administered as a single intravenous dose immediately before chemotherapy, followed by 4mg orally twelve hours later. 4mg orally twice daily should be continued for up to 5 days after a course of treatment.

Elderly:-
Zofran 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 the recommended oral dose is 16mg given one hour prior to anaesthesia.

For treatment of established post-operative nausea and vomiting Zofran administration by injection is recommended.

Children:-
For prevention and treatment of post-operative nausea and vomiting Zofran may be administered by injection.

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

PATIENTS WITH RENAL/HEPATIC IMPAIRMENT:

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

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.

Zofran Zydis contains aspartame and therefore should be taken with caution in patients with phenylketonuria.

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 and 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 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 (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥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 Zofran according to indication and formulation.

Immune system disorders
Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders
Very common: Headache.
Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae; seizures.
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 inpatients 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 Zofran itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-emetics and anti-nauseants

ATC code: A04A A01

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

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 (5h) 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 2mg (3-7 years old) or 4mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300ml/min at 12 years of age to 100ml/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 15-60ml/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 with prolonged elimination half-lives (15-32h) 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

Gelatin
Mannitol (E421)
Aspartame (E951)
Sodium methyl hydroxybenzoate (E219)
Sodium propyl hydroxybenzoate (E217)
Strawberry flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Store in the original package.
Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of 10 oral lyophlisates contained in an outer cardboard carton.

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

Do not attempt to push Zofran Zydis through the lidding foil. Peel back the lidding foil of on blister and gently remove the Zofran Zydis.
Place the Zofran Zydis on top of the tongue, where it will dissolve within seconds, then swallow.

7 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
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8 Parallel Product Authorisation Number

PPA 0465/113/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 16 June 2006

10 DATE OF REVISION OF THE TEXT

October 2008