SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zofran 16 mg Suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 16.00 mg of ondansetron.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories.
White, smooth, homogeneous suppository with a torpedo shape.

4. CLINCAL PARTICULARS

4.1 Therapeutic Indications

Zofran Suppositories are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

4.2 Posology and Method of Administration

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

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV and RINV):

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

CINV and RINV in Adults:
The recommended dose of Zofran Suppositories is one 16mg suppository given 1-2 hours before treatment.

To protect against delayed or prolonged emesis after the first 24 hours, rectal treatment with Zofran should be continued for up to 3 days, or oral treatment for up to 5 days after a course of treatment. The recommended daily dose of Zofran Suppositories is one 16mg suppository.

Paediatric Population:

CINV in Children and Adolescents (aged 6 months to 17 years)
The use of Zofran Suppositories in children is not recommended.

The usual method of administration is a single intravenous dose 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.

In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid (see section 6.6 Instructions for Use and Handling) and infused over not less than 15 minutes.

CINV and RINV in Elderly:
Zofran is well tolerated by patients over 65 years of age..

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 Zofran 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 IV or oral 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 Contra-indications

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see Section 5.1 Pharmacodynamic Properties – QT prolongation). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

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

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.

Paediatric Population

Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

Chemotherapy-induced nausea and vomiting:-

When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5 mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicate similar efficacy for both regimens (section 5.1).

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 interactions when ondansetron is administered with alcohol, temazepam, frusemide, alfentanil, tramadol, morphine, lignocaine, thiopental 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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval (including some Cytotoxics) and/or cause electrolyte abnormalities. (see section 4.4).

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias. (see section 4.4).

Serotonergic Drugs (e.g., SSRIs and SNRIs)

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs) (See section 4.4).

Apomorphine
Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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

Safety data of ondansetron in pregnancy are limited, and findings from available pharmaco-epidemiologic studies are inconsistent. Post-marketing reports describe cases of congenital malformations with use of Zofran during pregnancy; however the reports are insufficient to establish a causal relationship.
Reproductive studies in rats and rabbits did not show evidence of harm to the foetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively.. However as animal studies are not always predictive of human response the use of Zofran is not recommended during pregnancy and in women of childbearing potential not using contraception

Pregnancy testing
Pregnancy status should be verified in womend of child-bearing potential prior to starting the treatment with Zofran.

Breast-feeding
There is insufficient information on the excretion of ondasetron/metabolites in human milk or the effects of Zofran on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of ondansetron/metabolites in milk (for details see 5.3). A risk to the newborns/infants cannot be excluded. Zofran should not be used during breast-feeding.

Fertility
There are no data on the effects of ondansetron on human fertility.

4.7 Effects on Ability to Drive and Use Machines

Zofran has no or negligible influence on the ability to drive and use machines.
In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

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). 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. The adverse event profiles in children and adolescents were comparable to that seen in adults.

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)[1]
Rare: Dizziness predominantly during rapid IV administration.

Eye disorders
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during rapid intravenous administration.
Very rare: Transient blindness predominantly during intravenous administration[2].

Cardiac disorders
Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare: QTc prolongation (including Torsades de Pointes)

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[3].

Skin and subcutaneous tissue disorders
Very rare: Toxic skin eruption, including toxic epidermal necrolysis.

General disorders and administration site conditions
Common: Local IV injection site reactions.

[1] Observed without definitive evidence of persistent clinical sequelae.

[2] 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.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and Signs
There is limited experience of Zofran overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see section *4.8 Undesirable Effects*). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

Treatment
There is no specific antidote for Zofran, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The use of ipecacuanha to treat overdose with Zofran 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

Mechanism of action
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.

Ondansetron does not alter plasma prolactin concentrations

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Paediatric Population

Chemotherapy induced nausea and vomiting
The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 IV + ondansetron 4 mg orally after 8-12 hours or ondansetron 0.45 mg/kg IV + placebo orally after 8-12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m^2 IV + ondansetron 4 mg orally) and 41% (0.45 mg/kg IV + placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m^2 IV together with 2-4 mg dexamethasone orally.
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2-4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of IV ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hour after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one IV dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. Of children n=28). Complete control of emesis was achieved in 42% of patients.

5.2 Pharmacokinetic Properties

Following administration of an Ondansetron Suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The half-life of the elimination phase is determined by the rate of ondansetron absorption, not systemic clearance, and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender.

Ondansetron is not highly protein bound (70-76%) and 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.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults.

In patients with moderate renal impairment (creatinine clearance 15-60ml/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 pharmocokinetics to be essentially unchanged following intravenous administration.

Specific studies in the elderly or patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron in these populations will be similar to that in healthy volunteers since the rate of elimination of ondansetron following administration of a suppository is not determined by systemic clearance.

The pharmacokinetics of ondansetron following administration as a suppository has not been evaluated in patients with hepatic impairment.

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 at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see Section 5.1 Pharmacodynamic Properties – QT prolongation).

In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hard Fat
Cetomacrogol 1,000
Glyceryl ricinoleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

Do not store above 30°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and Contents of Container

Zofran suppositories are packaged in individually sealed cavities formed from a foil laminate, enclosed in a perforated cardboard mount and packed into a carton.

Zofran suppositories are available in pack sizes of one suppository.

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

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

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
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Elm Park

Merrion Road
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