1. NAME OF THE MEDICINAL PRODUCT

ZOFDAN (Ondansetron Tablets BP 4mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Ondansetron Hydrochloride BP	
Eq. to Ondansetron	4 mg
Excipients	q.s.
Approved colour used	

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Ondansetron is indicated for the prevention of post-operative nausea and vomiting (PONV).

For treatment of established PONV, administration by injection is recommended. **Paediatric Population:**

Ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months.

No studies have been conducted on the use of orally administered ondansetron in the prevention and treatment of PONV in children aged ≥ 1 month, administration by IV injection is recommended for this purpose.

4.2 Posology and Method of Administration

Posology

Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV)

Adults

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.

Emetogenic chemotherapy and radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

The recommended oral dose is 8 mg taken 1-2 hours before chemotherapy or radiation treatment, followed by 8 mg every12 hours for a maximum of 5 days to protect against delayed or prolonged emesis.

For highly emetogenic chemotherapy a single dose of up to 24 mg ondansetron taken with 12 mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron may be continued for up to 5 days after a course of treatment.

The recommended dose for oral administration is 8 mg to be taken twice daily.

Paediatric population

CINV in children and adolescents (aged 6 months to 17years)

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. In paediatric clinicalstudies, ondansetron was given by IV infusion diluted in 25 to 50 mL of saline or other compatible infusion fluid and infusedover not less than 15 minutes.

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged CINV.

There are no data from controlled clinical trials on the use of ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m2. The single intravenous dose must not exceed 8 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 1).

The total dose over twenty-four hours (given as divided doses) must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for CINV (aged ≥ 6 months to 17 years)

BSA	**Day 1 (a, b)**	**Days 2-6 (b)**
< 0.6 m2	5 mg/m2 IV plus 2 mg syrup after 12 hours	2 mg syrup every 12 hours
≥ 0.6 m2 to ≤ 1.2 m2	5 mg/m2 IV plus 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours
> 1.2 m2	5 mg/m2 or 8 mg IV plus 8 mg syrup or tablet after 12 hours	8 mg syrup or tablet every 12 hours

a. The intravenous dose must not exceed 8 mg.

b. The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Dosing by body weight

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The single intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals.

The total dose over twenty-four hours (given as divided doses) must not exceed adult dose of 32 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days.

Weight	Day 1 (a, b)	Days 2-6 (b)
≤ 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4hours	2 mg syrup every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4hours	4 mg syrup or tablet every 12 hours

a. The intravenous dose must not exceed 8 mg.

b. The total dose over twenty-four hours (given as divided doses) must not exceed adult dose of 32 mg.

Elderly

No alteration of oral dose or frequency of administration is required.

Renal impairment

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

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 is required.

Post-operative nausea and vomiting (PONV)

Adults

For the prevention of PONV*:* Ondansetron can be administered orally or by intravenous or intramuscular injection.

The recommended oral dose is 16 mg taken one hour prior to anaesthesia.

For the treatment of established PONV*:* Intravenous or intramuscular administration is recommended.

Paediatric population

PONV in children and adolescents (aged 1 month to 17 years)

Oral formulation

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow IV injection (not less than 30 seconds) is recommended for this purpose.

Injection

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) 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 PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4 mg.

There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

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.

Renal impairment

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

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 is required.

Method of Administration

The tablets should be swallowed whole with liquid.

4.3 Contraindications

Concomitant use with apomorphine is contraindicated.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special Warning and Precautions for Use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 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. 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 othermedicinal products that lead to QT prolongation or electrolyte abnormalities.Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in thecase of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients shouldbe alerted to the signs and symptoms of myocardial ischaemia. Hypokalemia and hypomagnesaemia 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 otherserotonergic 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 subacute 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.

CINV

When calculating the dose on an mg/kg basis and administering three doses at 4-hour 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 indicates similar efficacy for both regimens.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorptionshould 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 coadministered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities.

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 trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias.

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).

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 Pregnancy and Lactation

Women of childbearing potential

Women of childbearing potential should consider the use of contraception.

Pregnancy

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Ondansetron should not be used during the first trimester of pregnancy.

Breast-feeding

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.

Fertility

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on Ability to Drive and Use Machines

Ondansetron 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 suchactivities are predicted from the pharmacology of ondansetron.

4.8 Undesirable Effecsts

Adverse events are listed below by system organ class and absolute frequency (all reported events). Frequencies are defined as:

not known (cannot be estimated from the available data)

Very common, common and uncommon adverse reactions were generally determined from clinical trial data. The incidence of adverse reactions with placebo was taken into account.

Rare and very rare adverse events were generally determined from post-marketing spontaneous

data.

The following frequencies were determined with standard ondansetron dosing.

Immune system disorders

Rare: Immediate hypersensitivity reactions (sometimes severe), including

anaphylaxis.

Anaphylaxis can be life-threatening. Hypersensitivity reactions have also been observed in patients who have shown such phenomena with other selective 5-HT3 antagonists.

Nervous system disorders

Very common: Headache

Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, acute spasmodic oculomotor disorders with gaze deviation [oculogyric crisis] and dyskinesias), but without demonstrable long-term clinical

sequelae

Rare: Light-headedness, mainly with rapid IV administration

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during

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 on the ECG, bradycardia

Rare: QTc prolongation (including torsade de pointes)

Not known: Myocardial ischemia

Vascular disorders

Common: Sensation of warmth or flushing

Uncommon: Hypotension (fall in blood pressure)

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups

Gastrointestinal disorders

Common: Constipation

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests*

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

Skin and subcutaneous tissue disorders

Very rare: Toxic skin eruptions, including toxic epidermal necrolysis

Children and adolescents

The adverse reaction profile in children and adolescents was comparable to the adverse reaction profile observed in adults.

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. Healthcareprofessionals are asked to report any suspected adverse reactions via Appendix V.

4.9 Overdose

Symptoms and Signs

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). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block. Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Management

There is no specific antidote for ondansetron, therefore in all 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 ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Serotonin (5HT3) antagonist ATC code: A04AA01

Mode of action:

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 in 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 withcytotoxic induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established

5.2 Pharmacokinetic properties

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate

conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron. In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, Cmax, and t½ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron. Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important

5.3 Preclinical Safety Data

No additional data of relevance

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Lactose BP
- Microcrystalline Cellulose BP
- Povidone BP
- Purified Talc BP
- Magnesium Stearate BP
- Croscarmellose Sodium BP
- Colloidal Anhydrous Silica BP
- Crospovidone BP
- AF-Coat White IH

- Isopropyl Alcohol BP
- Dichloromethane BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

<36 Months>

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30°C. Protect from light.

Keep all medicines out of reach of the children.

6.5 Nature and Contents of Container <and Special Equipment for use, Administration or Implantation>

10 ×10 Tablets packed in a carton along with pack insert.

6.6 Special Precautions for Disposal <and Other Handling>

No special requirements.

7.0 Applicant/Sole Agent

Embassy Pharmaceutical & Chemical Ltd.

41, Ademola Street, South West Ikoyi, Lagos, Nigeria.

Manufacturer

Laborate Pharmaceuticals India Limited

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