For the Use of Registered Medicinal Practitioners or a Hospital or a Laboratory only

ONDEM-MD 4 mg /8 mg

1. Name of the medicinal product

ONDEM-MD (Ondansetron Orally Disintegrating Tablets USP 4 mg and 8 mg)

2. Qualitative and quantitative composition

3. Pharmaceutical form

Orally disintegrating Tablets

4. Clinical particulars

4.1 Therapeutic indications

Adults:

- Prophylaxis of acute nausea and vomiting induced by moderately emetogenic chemotherapy.
- Prophylaxis and treatment of delayed nausea and vomiting induced by moderately to highly emetogenic chemotherapy.
- Prophylaxis and treatment of acute and delayed nausea and vomiting induced by highly emetogenic radiotherapy.
- Prophylaxis and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:

- Management of chemotherapy-induced nausea and vomiting in children aged ≥6 months.
- Prophylaxis and treatment of post-operative nausea and vomiting (PONV) in children aged ≥4 years.

4.2 Posology and method of administration

4.2.1 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 selection of dose regimen should be determined by the severity of the emetogenic challenge.

Emetogenic chemotherapy and radiotherapy

Ondansetron is an oral formulation. The recommended oral dose is 8mg 1 to 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 dosage is 8mg to be taken twice daily.

Highly emetogenic chemotherapy (e.g. high dose cisplatin)

The recommended oral dose is 24 mg taken together with oral dexamethasone sodium phosphate 12mg, 1 to 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 dosage is 8mg to be taken twice daily.

Paediatric Population

Chemotherapy induced nausea and vomiting (CINV)

The dose for CINV can be calculated based on body surface area (BSA) or weight – see table 1 below. 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 or on the use of ondansetron for radiotherapy-induced nausea and vomiting (RINV) in children.

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

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

The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA and weight based dosing for Chemotherapy

BSA	**Day 1[a,b]**	**Day 2-6[b]**
<0.6m^2	5 mg/m^2 i.v*plus 2 mg** orally after 12 hrs	2 mg** orally every 12 hrs
≥0.6m^2	5 mg/m^2 i.v* plus 4 mg orally after 12 hrs	4 mg orally every 12 hrs
Weight	**Day 1[a,b]**	**Day 2-6[b]**
≤10 kg	Up to 3 i.v* doses of 0.15mg/kg every 4 hrs	2 mg** orally every 12 hrs
>10 kg	Up to 3 i.v* doses of 0.15mg/kg every 4 hrs	4 mg orally every 12 hrs

a The intravenous dose must not exceed 8 mg.

b The total daily dose must not exceed adult dose of 32 mg

*Ondem-MD is an oral preparation only, and is not available in an intravenous formulation

**Ondem-MD is only available as tablets of 4mg and 8mg. It is not possible to divide the tablet to obtain a 2 mg dosage.

Elderly

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

Prescribers intending to use ondansetron in the prevention of delayed nausea and vomiting associated with chemotherapy or radiotherapy in adults, adolescents or children should take into consideration current practice and appropriate guidelines.

Post-operative nausea and vomiting (PONV)

Adults

Prevention of Post-operative nausea and vomiting (PONV)

For the prevention of post-operative nausea and vomiting, the recommended oral dose is 16mg given 1 hour prior to anaesthesia.

Alternatively, use 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg at eight hourly intervals.
Treatment of established Post-operative nausea and vomiting (PONV)
For the treatment of established PONV, intravenous or intramuscular administration is recommended.
Treatment of established Post-operative nausea and vomiting (PONV)
For the treatment of established PONV, intravenous or intramuscular administration is recommended.

Paediatric population:

Post-operative nausea and vomiting
For the prevention and treatment of PONV, slow intravenous injection is recommended.
Alternatively, for administration in children weighing ≥ 40kg ondansetron can be administered orally as a 4 mg dose, one hour prior to anaesthesia, followed by one further dose of 4 mg after 12 hours.
There are no data on the use of ondansetron for the treatment of PONV in children under 2 years of age**.**
Elderly:
There is limited experience in the use of ondansetron in the prevention and treatment of PONV in the elderly; however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Special populations – both indications:

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 is required**.**

4.3 Contraindications
Hypersensitivity to ondansetron or to other selective 5-HT3-receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients listed in section 6.1.
• Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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. 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 Clinical Pharmacology). 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 therefore be monitored following administration.

In patients with adeno-tonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron administration.

Paediatric Population:

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

Chemotherapy-induced nausea and vomiting:

When calculating the dose on a mg/kg basis and administering three doses at 4 hourly intervals, the total daily dose will be higher than if one single dose of 5mg/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

4.5 Interaction with other medicinal products and other forms of interaction

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

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicinal products commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lignocaine, thiopental or propofol.

Ondansetron is metabolized 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 (eg, 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.

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).

Phenytoin, carbamazepine and rifampicin; in patients treated with potent inducers of CYP3A4, 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.

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), antifungal agents (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias .

4.6 Pregnancy and lactation

Pregnancy

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 the 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.

Breastfeeding

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

Ondansetron has no or negligible influence on the ability to drive and use machines**.**

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 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 dystonic reactions, oculogyric crisis and dyskinesia have been observed without definitive evidence of persistent clinical sequelae).

Rare: Dizziness during rapid intravenous 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, bradycardia.
Rare: QTc prolongation (including Torsade de Pointes)
Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.
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.
Paediatric Population
The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose
Little is known at present about over-dosage with ondansetron, however, a limited number of patients received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and vaso-vagal episodes with transient second degree AV block. In all instances, the events resolved completely.
Ondansetron prolongs QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.
There is no specific antidote for ondansetron, therefore in all 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 itsel**f.**
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
Pharmaco-therapeutic group: Anti-emetics and anti-nauseants, Serotonin (5-HT3) antagonists
ATC Code: A04AA01
Ondansetron is a potent, highly selective 5-HT3 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.
The role of ondansetron in opiate-induced emesis is not yet established.

The effect of ondansetron on the QTc interval was evaluated in a double-blind, randomised, 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. On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 intravenously + ondansetron 4 mg orally after 8-12 hrs; or ondansetron 0.45 mg/kg intravenous + placebo orally after 8-12 hrs. Post-chemotherapy both groups received 4 mg ondansetron orally twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m^2 intravenously + ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenously + 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 in 438 patients aged 1 to 17 years demonstrated complete control of emesis on the worst day of chemotherapy in:
• 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m^2 intravenous together with 2-4 mg dexamethasone orally
• 71% of patients when ondansetron was administered orally at a dose of 8 mg + 2 - 4 mg dexamethasone orally on the days of chemotherapy.
Post-chemotherapy both groups received 4 mg ondansetron orally twice daily for 2 days. There was no difference in the overall 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. All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 yrs and 8 mg for children aged ≥12 yrs (total number of children n= 28). Complete control of emesis was achieved in 42% of patients.

Prevention of post-operative nausea and vomiting

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥44 weeks, weight ≥3 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p <0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesic induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting.

5.2 Pharmacokinetic properties

Ondem-MD is an orodispersible tablet. Once in contact with saliva, it disintegrates in a few seconds.

Following oral administration of ondansetron, absorption is rapid with maximum peak plasma concentrations of about 30ng/ml being attained and achieved in approximately 1.5 hours after an 8mg dose. The syrup and tablet formulations are bioequivalent and have an absolute oral bioavailability of 60%.

The disposition of ondansetron following oral, intravenous and intramuscular dosing is similar with a terminal elimination half-life of approximately 3 hours and a steady-state volume of distribution of about 140L. 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 the pharmacokinetics of ondansetron. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Special Patient Populations

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 months 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. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In 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 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 approaching those of young adults. When clearance and volume of distribution values were normalized by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalizing systemic exposure in paediatric patients.
Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly

Studies in healthy elderly volunteers have shown a 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).

Renal impairment

In patients with renal impairment (creatinine clearance >15 ml/min), 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.

Hepatic impairment

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32h) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.
Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 5.2:1.
A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

24 Months

6.2 Special precautions for storage
Store below 30^{O} C. Protect from light & moisture.

6.3 Nature and contents of container
Ondansetron Orally Disintegrating Tablets USP are presented in 1x10s strip pack.

7. Marketing authorization holder

ALKEM LABORATORIES LTD.
Alkem House, Senapati Bapat Marg,
Lower Parel, Mumbai-400 013

8. DATE OF REVESION OF TEXT
September 2017.

3.2.2.9.5 Patient Information leaflet

Enclosed in subsequent pages.

PATIENT INFORMATION LEAFLET

1. Product name

ONDEM-MD 4/8 (Ondansetron Orally Disintegrating Tablets USP 4 mg and 8 mg)

2. Recommendations as:

Keep this leaflet. You may need to read it again.

- Read the instruction carefully before use
- Keep out of reach of children
- If you have any further questions about your illness or your medicine, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

3. Ingredients; strength / concentration

ONDEM-MD 4

Label claim:

Each uncoated tablet contains ondansetron USP… 4 mg

Colour: Sunset Yellow Lake

ONDEM-MD 8

Label claim:

Each uncoated tablet contains ondansetron USP… 8 mg

Colour: Sunset Yellow Lake

4. Description of finished product

ONDEM-MD 4

Description: Light orange coloured, circular, flat beveled edges uncoated tablets having break line on one side and plain on other side.

ONDEM-MD 8

Description: Light orange coloured, circular, biconvex uncoated tablets having break line on one side and plain on other side.

5 Pack Size;

Ondansetron Orally Disintegrating Tablets USP are presented in 1x10s strip pack.

6 What is this medicine used for?

Ondem belongs to a group of medicines called anti-emetics.

Ondem tablets are used for:

- preventing nausea and vomiting caused by chemotherapy (in adults and children) or radiotherapy for cancer (adults only)
- preventing nausea and vomiting after surgery (adults only).

Ask your doctor, nurse or pharmacist if you would like any further explanation about these uses.

7 How much and how often should you use this medicine?

Always take Ondansetron Orally Disintegrating Tablets USP exactly as your doctor has told you. You should check with your doctor, nurse or pharmacist if you are not sure. The dose you have been prescribed will depend on the treatment you are having.

<u>To prevent nausea and vomiting from chemotherapy or radiotherapy</u>

On the day of chemotherapy or radiotherapy

- the usual adult dose is 8 mg taken one to two hours before treatment and another 8 mg twelve hours after.

On the following days:

- the usual adult dose is 8 mg twice a day
- this may be given for up to 5 days.

Children aged over 6 months and adolescents

The doctor will decide the dose depending on the child's size (body surface area) or weight. Look at the label for more information.

- the usual dose for a child is up to 4 mg twice a day
- this can be given for up to 5 days.

To prevent nausea and vomiting after an operation

- The usual adult dose is 16 mg before your operation

9 Undesirable effect / adverse reaction

Like all medicines, Ondansetron Orally Disintegrating Tablets USP can cause side effects, although not everybody gets them.

Allergic reactions

If you have an allergic reaction, stop taking it and see a doctor straight away. The signs may include:

- sudden wheezing and chest pain or chest tightness
- swelling of your eyelids, face, lips, mouth or tongue
- skin rash - red spots or lumps under your skin (hives) anywhere on your body
- collapse.

Other side effects include:

Very common (may affect more than 1 in 10 people)

- headache.

Common (may affect up to 1 in 10 people)

- a feeling of warmth or flushing
- constipation
- changes to liver function test results (if you take Ondansetron Orally Disintegrating Tablets USP with a medicine called cisplatin, otherwise this side effect is uncommon).

Uncommon (may affect up to 1 in 100 people)

- hiccups
- low blood pressure, which can make you feel faint or dizzy
- uneven heart beat
- chest pain
- fits
- unusual body movements or shaking.

Rare (may affect up to 1 in 1,000 people)

- feeling dizzy or light headed
- blurred vision
- disturbance in heart rhythm (sometimes causing a sudden loss of consciousness)

Very rare (may affect up to 1 in 10,000 people)

- poor vision or temporary loss of eyesight, which usually comes back within 20 minutes.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly to Ministry of Health. By reporting side effects you can help provide more information on the safety of this medicine.

10 What other medicine or food should be avoided whilst taking this medicine?

Please tell your doctor, nurse or pharmacist if you are taking or have recently taken or might take other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Ondansetron can affect the way some medicines work. Also some other medicines can affect the way Ondansetron works. In particular, tell your doctor, nurse or pharmacist if you are taking any of the following medicines:

- Carbamazepine or phenytoin used to treat epilepsy
- Rifampicin used to treat infections such as tuberculosis (TB)
- Antibiotics such as erythromycin or ketoconazole
- Anti-arrhythmic medicines used to treat an uneven heart beat
- Beta-blocker medicines used to treat certain heart or eye problems, anxiety or prevent migraines
- Tramadol, a pain killer
- Medicines that affect the heart (such as haloperidol or methadone)
- Cancer medicines (especially anthracyclines and trastuzumab).
- SSRIs (selective serotonin reuptake inhibitors) used to treat depression and/or anxiety including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram
- SNRIs (serotonin noradrenaline reuptake inhibitors) used to treat depression and/or anxiety including venlafaxine, duloxetine.

If you are not sure if any of the above applies to you, talk to your doctor, nurse or pharmacist before having Ondansetron Orally Disintegrating Tablets USP.

11 What should you do if you miss a dose?

If you miss a dose and feel sick or vomit:

- take Ondansetron Orally Disintegrating Tablets USP as soon as possible, then
- take your next tablet at the usual time (as shown on the label)
- do not take a double dose to make up for a forgotten dose.

If you miss a dose but do not feel sick

- take the next dose as shown on the label
- do not take a double dose to make up for a forgotten dose.

12 How should you keep this medicine?

- Keep this medicine out of the sight and reach of children.
- Do not use Ondansetron Orally Disintegrating Tablets USP after the expiry date. The expiry date refers to the last day of that month.
- Store Ondansetron Orally Disintegrating Tablets USP below 30^{O} C. Protect from light & moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

13 Signs & Symptoms of overdosage

There is limited experience of ondansetron overdose. In the majority of cases, symptoms are similar to those already reported in patients receiving recommended doses. Some features of overdose that have been reported include visual disturbances, severe constipation, reduction ion blood pressure (hypotension) and an episode of transient loss of consciousness (vasovagal episode). Ondansetron may interfere with the conduction of impulses in the heart and cause problems with the rhythm of heart contraction in a dose-dependent fashion. Thus, ECG monitoring is recommended in cases of overdose.

14 What to do when you have taken more than the recommended dosage?

If you or your child take more Ondansetron than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

15 Care that should be taken when taking this medicine?

Always take Ondansetron Orally Disintegrating Tablets USP exactly as your doctor has told you. You should check with your doctor, nurse or pharmacist if you are not sure. The dose you have been prescribed will depend on the treatment you are having.

Do not take Ondansetron Orally Disintegrating Tablets USP if:

- you are taking apomorphine (used to treat Parkinson's disease)

- you are allergic (hypersensitive) to ondansetron or any of the other ingredients in Ondansetron Orally Disintegrating Tablets USP .

If you are sick (vomit) within one hour of taking a dose

- take the same dose again
- otherwise, do not take more Ondansetron Orally Disintegrating Tablets USP than the label says.

If you continue to feel sick, tell your doctor or nurse.

Warnings and precautions

Check with your doctor, nurse or pharmacist before taking Ondansetron Orally Disintegrating Tablets USP if:

- you have ever had heart problems (e.g. congestive heart failure which causes shortness of breath and swollen ankles)
- you have an uneven heart beat (arrhythmias)
- you are allergic to medicines similar to ondansetron, such as granisetron or palonosetron
- you have liver problems
- you have a blockage in your gut
- you have problems with the levels of salts in your blood, such as potassium, sodium and magnesium.
- If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before taking Ondansetron Orally Disintegrating Tablets USP .

Pregnancy and breast-feeding

It is not known if Ondansetron is safe during pregnancy. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking Ondansetron Orally Disintegrating Tablets USP . Do not breast-feed if you are taking Ondansetron. This is because small amounts pass into the mother's milk. Ask your doctor or midwife for advice.

Important information about some of the ingredients of Ondansetron Orally Disintegrating Tablets USP : This medicine does not contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, speak to your doctor before taking this medicine.

Patients with moderate or severe liver problems: The total daily dose should not be more than 8 mg.

16 When should you consult your doctor, pharmacist?

Talk to your doctor or pharmacist if:

- You are not sure about the dose of medicine that is appropriate for you
- You continue to feel sick even after taking two doses of ondansetron
- Are suffering from liver disease
- Are pregnant or planning to become pregnant while on ondansetron therapy
- You are suffering from any of the conditions mentioned in the section "warning and precautions"

17 Shelf-life of product

24 Months

18 Name, address & logo (if any) of Manufacturer

ALKEM LABORATORIES LTD.

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19 Date of revision PIL

Sep. 2017