SUMMARY OF PRODUCT CHARACTERISTICS
ONDEX MD (Ondansetron Orally Disintegrating Tablets USP 8 mg)

1. NAME OF THE MEDICINAL PRODUCT

ONDEX MD (Ondansetron Orally Disintegrating Tablets USP 8 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orally disintegrating tablet contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate).

Excipients with known effect:

Aspartame (E951): present in each tablet. Patients with phenylketonuria should be aware of the aspartame content (see section 4.4).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orally disintegrating tablet.

White coloured, round, uncoated tablet with a break-line on one side and plain on the other side. The tablet disperses within seconds when placed on the tongue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ONDEX MD is indicated for:

- Prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
- Prevention of post-operative nausea and vomiting (PONV).

4.2 Posology and method of administration

Method of administration

For oral use. Place the ONDEX MD tablet on top of the tongue, where it will disperse within seconds, then swallow. The tablet may also be taken with a drink of water. Ondansetron is also available for parenteral use to allow flexible route of administration and dosing.

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 8 mg 1–2 hours before treatment, followed by 8 mg orally 12 hours later. To protect against delayed or prolonged emesis after the first 24 hours, oral treatment should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg twice daily.

Highly emetogenic chemotherapy:

Ondansetron can be given by oral, intravenous or intramuscular administration. For patients receiving highly emetogenic chemotherapy, an initial intravenous or intramuscular dose may be considered, followed by oral dosing. To protect against delayed or prolonged emesis after the first 24 hours, oral treatment should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg twice daily.

Children and adolescents (aged 6 months to 17 years):

In children with a body surface area of 0.6 to 1.2 m^2, ondansetron is administered as a single intravenous dose of 5 mg/m^2 immediately before chemotherapy, followed by 4 mg orally twelve hours later. 4 mg orally twice daily can be continued for up to 5 days after a course of treatment.

For children with a body surface area greater than 1.2 m^2, an initial intravenous dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8 mg orally twice daily can be continued for up to 5 days after a course of treatment.

Alternatively, in children aged 6 months or older, ondansetron is administered as a single intravenous dose of 0.15 mg/kg (not to exceed 8 mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of 3 doses. 4 mg orally twice daily can be continued for up to 5 days after a course of treatment. Adult doses must not be exceeded.

Elderly:

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

Post-operative nausea and vomiting (PONV)

Adults:

For prevention of PONV, the recommended oral dose is 16 mg given one hour prior to anaesthesia. For treatment of established PONV, ondansetron administration by injection is recommended.

Children and adolescents (aged 1 month to 17 years):

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of PONV in children. Slow intravenous injection is recommended for this purpose.

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

Patients with renal impairment:

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

Patients with hepatic impairment:

Clearance of ondansetron is significantly reduced and serum half-life is significantly prolonged in subjects with moderate or severe hepatic impairment. 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.

4.3 Contraindications

- Hypersensitivity to ondansetron or to other selective 5-HT_3-receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients listed in section 6.1.
- Concomitant use with apomorphine. Co-administration of ondansetron and apomorphine has been associated with profound hypotension and loss of consciousness. This interaction is considered clinically significant and therefore the use of ondansetron in patients receiving apomorphine is contraindicated (see section 4.5).
- Congenital long QT syndrome (see section 4.4).

4.4 Special warnings and precautions for use

QT prolongation and cardiac arrhythmias

Ondansetron prolongs the QT interval in a dose-dependent manner. Cases of Torsades de Pointes have been reported in patients receiving ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. ONDEX MD should be administered with caution to patients who have or may develop prolongation of the QT interval. This includes patients with hypokalaemia, hypomagnesaemia, congestive heart failure, bradyarrhythmias, or patients who are taking concomitant medicinal products that prolong the QT interval (see section 4.5). Electrolyte disturbances such as hypokalaemia and hypomagnesaemia should be corrected prior to administering ondansetron.

Serotonin syndrome

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following concomitant use of serotonergic drugs including selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of the patient is advised.

Hypersensitivity reactions

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. These reactions may be severe in nature. Patients who experience a hypersensitivity reaction should not be re-exposed to ondansetron.

Subacute intestinal obstruction

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

Aspartame — Phenylketonuria

ONDEX MD orally disintegrating tablets contain aspartame, a source of phenylalanine. This may be harmful to patients with phenylketonuria. Patients with this condition should be advised to monitor total daily phenylalanine intake.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

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 drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol 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.

Apomorphine:

Concomitant use of apomorphine and ondansetron is contraindicated. Co-administration has been associated with profound hypotension and loss of consciousness (see section 4.3).

QT-prolonging medicinal products:

Concomitant administration of ondansetron with other medicinal products known to prolong the QT interval and/or cause electrolyte disturbances (e.g. class IA and III antiarrhythmics, antipsychotics, tricyclic antidepressants, some antimicrobials, and antifungals such as ketoconazole) may increase the risk of ventricular arrhythmias, including Torsades de Pointes. Caution is required and electrocardiographic monitoring should be considered (see section 4.4).

Serotonergic drugs:

The co-administration of ondansetron with serotonergic agents including SSRIs (e.g. fluoxetine, paroxetine), SNRIs (e.g. venlafaxine, duloxetine), MAOIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, and mirtazapine may increase the risk of serotonin syndrome. If concomitant treatment is clinically warranted, careful observation of the patient is advised (see section 4.4).

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. Dose adjustment may be required in patients on potent CYP3A4 inducers.

Tramadol:

Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

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 only be used during the first trimester of pregnancy if the benefits of use clearly outweigh the risks of harm to the woman and the foetus. Ondansetron should be avoided during the second and third trimesters unless clearly necessary. If used during the third trimester, the newborn should be monitored for neonatal withdrawal symptoms.

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

Animal studies have not shown evidence of impaired fertility with ondansetron at therapeutically relevant exposures. There are no clinical data on the effect 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. However, patients should be informed that dizziness has been reported uncommonly with ondansetron and should be cautioned accordingly.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reaction with ondansetron is headache. Constipation and sensation of warmth or flushing are also common.

Tabulated list of adverse reactions

Adverse events are listed below by MedDRA System Organ Class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000) including isolated reports.

Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from post-marketing spontaneous data.

System Organ Class	Very common ≥1/10	Common ≥1/100	Uncommon ≥1/1,000	Rare ≥1/10,000	Very rare <1/10,000
Immune system disorders				Immediate hypersensitivity reactions including anaphylaxis	
Nervous system disorders	Headache		Seizures Movement disorders (incl. extrapyramidal reactions: oculogyric crisis, dystonic reactions, dyskinesia)	Dizziness (during rapid i.v. administration)	Serotonin syndrome (in combination with serotonergic drugs)
Eye disorders				Transient visual disturbances (e.g. blurred vision), predominantly during i.v. administration	Transient blindness predominantly during i.v. administration (majority resolved within 20 min)
Cardiac disorders			Arrhythmias Chest pain with or without ST segment depression Bradycardia		Torsades de Pointes QT interval prolongation
Vascular disorders		Sensation of warmth or flushing	Hypotension		
Respiratory, thoracic and mediastinal disorders			Hiccups		
Gastrointestinal disorders		Constipation Diarrhoea			

System Organ Class	Very common ≥1/10	Common ≥1/100	Uncommon ≥1/1,000	Rare ≥1/10,000	Very rare <1/10,000
Hepatobiliary disorders		Transient asymptomatic increases in liver enzyme values (primarily in patients receiving cisplatin-containing chemotherapy)			
Skin and subcutaneous tissue disorders			Rash		
General disorders					

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 the National Regulatory Authority.

4.9 Overdose

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). There is no specific antidote for ondansetron; therefore, in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. The possibility of QT interval prolongation should be considered in any patient presenting with overdose. Cardiac monitoring should be provided.

The use of ipecacuanha to treat overdose with ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-emetics and anti-nauseants; Serotonin (5-HT_3) receptor antagonists. ATC Code: A04AA01.

Mechanism of action

Ondansetron is a potent, highly selective 5-HT_3 receptor antagonist. Its precise mode of action in the control of nausea and vomiting is not fully established. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine, initiating a vomiting reflex by activating vagal afferents via 5-HT_3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT in the area postrema, located on the floor of the fourth ventricle, which may also promote emesis through a central mechanism. The effect of ondansetron in the management of chemotherapy and radiotherapy-induced nausea and vomiting is attributed to antagonism of 5-HT_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.

Cardiac electrophysiology

Ondansetron blocks cardiac HERG potassium channels in vitro. QT interval prolongation has been reported following clinical use. Clinicians should consider the cardiovascular risks before prescribing ondansetron, particularly at higher doses or in susceptible patients (see section 4.4).

5.2 Pharmacokinetic properties

General

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 8 mg, 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 is 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 a steady-state volume of distribution of about 140 L. 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 pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Gender differences

Gender differences have been 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). Studies in healthy elderly volunteers have shown slight but clinically insignificant age-related increases in both oral bioavailability and half-life of ondansetron.

Paediatric population

In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months but comparable to patients aged 3 to 12 years. The half-life in the 1 to 4 month patient population averaged 6.7 hours compared to 2.9 hours for patients aged 5 to 24 months and 3 to 12 years.

In a study of 21 paediatric patients aged between 3 and 12 years, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose were reduced in comparison to adult values. Both parameters increased in a linear fashion with weight, and by 12 years of age the values were approaching those of young adults. Use of weight-based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis confirmed that administration of a 0.15 mg/kg intravenous dose of ondansetron every 4 hours for 3 doses results in a systemic exposure (AUC) in children aged 1 month to 48 months comparable to that observed in older paediatric and adult populations at similar doses.

Special populations

Renal impairment: In patients with moderate renal impairment (creatinine clearance 15–60 ml/min), both systemic clearance and volume of distribution are reduced, resulting in a slight but clinically insignificant increase in elimination half-life (5.4 h). In patients with severe renal impairment requiring regular haemodialysis, ondansetron pharmacokinetics were essentially unchanged.

Hepatic impairment: In patients with severe hepatic impairment, ondansetron systemic clearance is markedly reduced with prolonged elimination half-lives (15–32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. A maximum total daily dose of 8 mg is recommended in these patients.

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 lactating rats; the milk/plasma ratio was 5.2:1. In vitro studies in cloned human cardiac ion channels have shown that ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is described in sections 4.4 and 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are present in each orally disintegrating tablet:

No.	Ingredient
1	Microcrystalline cellulose
2	Mannitol (pregelatinised)
3	Purified talc
4	Aspartame (E951) — excipient with known effect
5	Guar gum
6	Colloidal silica, anhydrous
7	Magnesium stearate

No.	Ingredient
8	Strawberry flavour
9	Sodium starch glycolate

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 and moisture. Keep out of the reach and sight of children.

6.5 Nature and contents of container
10 orally disintegrating tablets are packed in an aluminium blister; 3 blisters are packed in one mono-carton with package insert.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
NATIONAL PHARMACY LTD

P.O. Box 17843-00500, Nairobi, Kenya.

8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)
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