Prezinton
Solution for injection

Dexa Medica

Composition:
Each ml contains
Ondansetron HCl dihydrate equivalent to Ondansetron 2 mg

List of Excipients:
Sodium chloride, citric acid monohydrate, trisodium citrate dihydrate, water for injection.

Product Description:
Clear, colorless solution, free from visible particles.

Clinical Pharmacology:
ATC code: A04AA01
Pharmacotherapeutic group: serotonin ($5HT_3$ antagonist).

Mechanism of action
Ondansetron is a potent, highly selective $5HT_3$ receptor antagonist while precisely acting in control nausea and vomiting is not known.
Chemotherapeutic agents and radiotherapy may activate vagal afferents in the area postrema via $5HT_3$ receptors that cause release of 5HT in the small intestine and initiating a vomiting reflex. Ondansetron blocks the initiation of this reflex.
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 peripheral and central nervous system.
The mechanism of action of ondansetron in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

Pharmacodynamics
Ondansetron does not alter plasma prolactin concentrations.
The role of ondansetron in opiate-induced emesis is not yet established.

QT Prolongation
The effects of ondansetron on the QTc intervals 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.

Pharmacokinetics
The pharmacokinetic properties of ondansetron are unchanged on repeating dosing.
Absorption
Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

Distribution
The disposition of ondansetron following oral, intramuscular and intravenous dosing in adults is similar with a steady state volume of distribution about 140 liters. Ondansetron is not highly protein bound (70 to 76%).

Metabolism
Ondansetron is cleared from the systemic circulation predominantly through multiple enzymatic pathways in hepatic metabolism. The absence of CYP2D6 enzyme (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Elimination
The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal administration. Less than 5% of unchanged substance excreted in the urine.

Special patient populations
Gender
Female patients have a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution of ondansetron (adjusted for weight).

Children and adolescents (aged 2 years and over)
In paediatric patients (aged 3 to 12 years) undergoing elective surgery with general anaesthesia, the absolute values for both 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 normalised 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 normalising systemic exposure in paediatric patients.

Elderly
Early phase I studies in healthy elderly patients showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide intersubject variability resulted in considerable overlap in pharmacokinetic parameters between young (<65 years of age) and elderly patients (≥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. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see **Recommended Dosage — CINV and RINV**).

Renal impairment
In patients with moderate renal impairment (creatinine clearance 15 to 60 ml/minute), both systemic clearance and volume distribution are reduced following intravenous administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following intravenous administration.

Hepatic impairment
In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% due to reduced presystemic metabolism.

Indications:
Adults
PREZINTON is indicated for nausea and vomiting management induced by cytotoxic chemotherapy and radiotherapy.
PREZINTON is also indicated for postoperative nausea and vomiting prevention and treatment management.

Paediatric
PREZINTON is indicated for nausea and vomiting management induced by cytotoxic chemotherapy in children. There is no data on the use of oral administration of ondansetron in prevention or treatment management of postoperative nausea and vomiting. The intravenous administration is recommended for this purpose.

Recommended Dosage:
Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV)
The selection of dose regimen of ondansetron can be varied according to the emetogenic potentials of cancer treatment.

Adults
The recommended intravenous (IV) or intramuscular (IM) dose of ondansetron is 8 mg administered immediately before treatment.

For highly emetogenic chemotherapy, PREZINTON is administered in a maximum initial dose of 16 mg by intravenous infusion over 15 minutes. A single IV dose greater than 16 mg should not be given due to dose-dependent increase of QT prolongation risk (see **Warnings and Precautions, Adverse Effects, and Clinical Pharmacology — QT Prolongation**). The efficacy of PREZINTON in highly emetogenic chemotherapy may be enhanced by the addition of a single IV dose of dexamethasone sodium phosphate 20 mg, administered prior to chemotherapy.

IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 ml to 100 ml of 0.9% sodium chloride injection or 5% dextrose injection before administration and infused over not less than 15 minutes (see **Instructions for Use and Handling and Disposal**). PREZINTON doses of 8 mg or less, do not need to be diluted and may be administered as a slow IM or IV injection in not less than 30 seconds.

The initial dose of PREZINTON may be followed by 2 additional IV or IM doses of 8 mg by 2 to 4 hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Children and adolescents (aged 2 years and over)
Paediatric patients 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 prior chemotherapy, followed by 4 mg orally 12 hours later. Then 4 mg orally twice daily can be continued for up to five days after a course of treatment.

Elderly
In patient 65 to 74 years of age
The initial IV doses of PREZINTON 8 mg or 16 mg, infused over 15 minutes. The dose may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart. All IV doses should be diluted in 50–100 ml of saline or other compatible infusion fluid and infused over 15 minutes.

In patient 75 years of age or older
The initial intravenous dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by two additional intravenous doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart (see **Clinical Pharmacology – Elderly**). All intravenous doses should be diluted in 50–100 ml of saline or other compatible infusion fluid (see **Incompatibilities**) and infused over 15 minutes.

Postoperative nausea and vomiting (PONV)
Adults
For prevention of PONV, the recommended dose of PREZINTON injection is a single dose of 4 mg by intramuscular or slow intravenous injection administered at the induction of anaesthesia.
For treatment of established PONV, a single dose of 4 mg given by IM or slow IV injection is recommended.

Children and adolescents (aged 2 years and over)
For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, PREZINTON 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 or after surgery.
There are limited data about the use of ondansetron in the prevention and 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 elderly. However, ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Special populations
Patient with renal impairment
No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patient with hepatic impairment
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in patients with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8 mg intravenous or oral should not exceeded.

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in patients 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.

Route of Administration:
For intravenous injection (IV) or intramuscular injection (IM) or after dilution for intravenous infusion.

Contraindications:
- Hypersensitivity to ondansetron or any other selective $5HT_3$ receptors antagonist (e.g. granisetron, dolosetron) or any of the excipients in this product (see **List of Excipients**).
- Concomitant used of ondansetron with apomorphine hydrochloride is contraindicated since profound hypotension and loss of consciousness was reported (see **Interactions with Other Medicines and Other Forms of Interaction**).

Warnings and Precautions:
- Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptors antagonists including anaphylaxis and bronchospasm.
- Ondansetron prolongs the QT intervals in a dose-dependent manner (see **Clinical Pharmacology**). In addition, postmarketing cases of torsade de pointes have been reported in patients using ondansetron. Avoid ondansetron administration in patients with congenital long QT syndrome.
- Ondansetron should be administered with caution in 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. Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with antiarrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.
- Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms of myocardial ischemia appeared immediately after intravenous administration but recovered with prompt treatment. Therefore, caution should be exercised during and after the administration of ondansetron.

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- Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.
- Serotonin syndrome has been described following the concomitant use of ondansetron and other serotonergic drugs (see **Interactions with Other Medicines and Other Forms of Interaction**). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.
- Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impairment hepatic function.
- As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Interactions with Other Medicines and Other Forms of Interaction:
- Specific studies have shown that there are no pharmacokinetic 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 of the enzymes (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes. However, it should result in little or no significant change in overall ondansetron clearance or dose requirement.
- Use of ondansetron with QT prolonging drugs and/or drugs that cause electrolyte abnormalities may result in additional QT prolongation. PREZINTON concomitant use with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. Therefore, ondansetron should be administered with caution in patients treated with drugs that prolong the QT interval and/or cause electrolyte abnormalities and/or cardiotoxic drugs, because it may result in additional QT prolongation (see **Warnings and Precautions**).

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

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.

Serotonergic drugs
Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular abnormalities) has been described following the concomitant use of ondansetron and other serotonergic drugs, including selective reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see **Warnings and Precautions**). There are also reports of serotonin syndrome when ondansetron is used concomitantly with opioid/opiate medicines, e.g. buprenorphine.

Tramadol
Ondansetron may reduce the analgesic effect of tramadol.

Use during Pregnancy and Lactation:
Pregnancy
Risk summary
In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy (see *Human data*). Regarding cardiac malformations the epidemiological studies showed conflicting results.
Reproductive studies in rats and rabbits did not show evidence of harm to the fetus (see *Animal data*).
The use of ondansetron in pregnancy is not recommended.

Human data
Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy.
One cohort study with 88,467 pregnancies exposed to ondansetron showed an increased risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03–1.48)) without an apparent increase in risk of cardiac malformations.
A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations.
One case-control study using population-based birth defect registries with 23,200 cases across two datasets reported an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study.
The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95% CI 1.0–2.9), but no statistically significant increase in risk of cardiac malformations, adjusted RR 1.3 (95% CI 0.86–1.8).

Animal data
In embryo-fetal 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.

Lactation
Risk summary
It is not known whether ondansetron is transferred into human milk. There are no data on the effect of ondansetron on breastfed child or the effects of ondansetron on milk production. However, it has been demonstrated that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breastfeed their babies.

Females and males of reproductive potential
Pregnancy testing
Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with ondansetron.

Contraception
Females of reproductive potential should be advised that it is possible that ondansetron can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less 1% pregnancy rates) when using ondansetron during the treatment and for two days after stopping treatment with ondansetron.

Infertility
There is no effect of ondansetron on fertility.

Adverse Effects:
The following adverse effects are classified by system organ class and frequency. Frequencies are defined according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or not known (cannot be estimated).

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

System Organ Classification	Frequency	Adverse Effects
Gastrointestinal disorders	Common	constipation, local burning sensation following insertion of suppositories
Respiratory, thoracic, and mediastinal disorders	Uncommon	hiccups
Hepatobiliary disorders	Uncommon	asymptomatic increases in liver function test, these events were observed commonly in patients receiving chemotherapy with cisplatin
Vascular disorders	Common	sensation of warmth or flushing
	Uncommon	hypotension
Cardiac disorders	Uncommon	arrhythmias, chest pain with or without ST segment depression, bradycardia
	Rare	QTc prolongation (including torsade de pointes)
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 predominantly 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
Skin and subcutaneous tissue disorders	Very rare	toxic skin eruption (including toxic epidermal necrolysis)
General disorders and administration site conditions	Common	local intravenous injection site reactions

Adverse effects from spontaneous reports and literature cases (frequency not known)
The following adverse effects have been derived from postmarketing experience with ondansetron via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse effects are listed according to system organ classification.

Cardiac disorders
Myocardial ischemia.

Overdose and Treatment:
Symptoms and signs
There is limited experience of ondansetron overdose. In the majority of cases symptoms were similar to those already reported in patients who received recommended doses (see **Adverse Effects**). The manifestation included visual disturbances, severe constipation, hypotension, and a vasovagal episode with transient second-degree atrioventricular block (AV block). In all instances, the events resolved completely.
Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.
Cases consistent with serotonin syndrome have been reported in young children following oral overdose.

Treatment
There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
The use of ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the antiemetic action of ondansetron itself.

Incompatibilities
Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

Compatibility with intravenous fluid
Based on the study, ondansetron injection is stable for 24 hours in storage condition 30±2ºC and 2–8ºC after reconstituted with:
- 0.9% sodium chloride solution.
- 5% glucose solution.
- 20% mannitol solution.
- ringer lactate solution.
- 0.3% potassium chloride and 0.9% sodium chloride solution, or
- 0.3% potassium chloride and 5% glucose solution.

Instructions for Use and Handling and Disposal:
For single use only. Any unused solution should be discarded.
The solution should be visually inspected prior to use. Only clear and colourless solutions practically free from particles should be used.

PREZINTON injection should only be admixed with those infusion solutions which are recommended (see **Incompatibilities**).

In keeping with good pharmaceutical practice, IV solutions should be prepared at the time of infusion, under appropriate aseptic conditions.

Presentation and Registration Number:
Box, 5 glass type I clear ampoules x 2 ml; SINXXXXXX

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURES BELOW 30ºC, PROTECT FROM LIGHT.

Manufactured by
PT Ferron Par Pharmaceuticals
Cikarang-Indonesia

For
PT Dexa Medica
Jl. Jend. Bambang Utoyo No. 138
Palembang-Indonesia

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