Package leaflet: Information for the user

Ondansetron Vianex, Solution for injection 4 mg/2 ml
Ondansetron Vianex, Solution for injection 8 mg/4 ml

Ondansetron

Read all of this leaflet carefully before you start taking this medicine.

- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.**

What is in this leaflet:

1. WHAT ONDANSETRON VIANEX IS AND WHAT IT IS USED FOR

Ondansetron Vianex belongs to a group of medicines called anti-emetics. Some pharmaceutical substances or treatments can induce the release of a substance which may cause nausea and vomiting. Ondansetron Vianex inhibits the effect of this substance and thus prevents nausea or vomiting.

Adults: Ondansetron Vianex solution for injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron Vianex solution for injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Paediatric Population: Ondansetron Vianex is indicated for the management of chemotherapy-induced nausea and vomiting in children aged ≥ 6 months and for the prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE ONDANSETRON VIANEX

Do not take Ondansetron Vianex

- If you are allergic (hypersensitive) to ondansetron or any of the other ingredients of Ondansetron Vianex.

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

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

Rarely, transient ECG changes including QT interval prolongation have been reported to patients taking ondansetron. Furthermore, after marketing, incidents of polymorphic ventricular tachycardia (Torsade de Pointes) have been reported to patients taking ondansetron. Ondansetron should be

carefully administered to patients that have or could develop QTc prolongation. These circumstances include patients with electrolytic disturbances, congenital QT prolongation syndrome or patients that receive other medicines that cause QT prolongation.

As ondansetron increases large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following its administration.

In patients with adenotonsillar surgery, prevention of nausea and vomiting with Ondansetron Vianex 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.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

There is no evidence that ondansetron induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, 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.

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.

The use of Ondansetron Vianex with QT prolonging drugs may result in additional QT prolongation. Concomitant use of Ondansetron Vianex with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias.

Pregnancy and breast-feeding
The safe use of ondansetron during 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 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.

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.

Driving and using machines
In psychomotor testing ondansetron does not impair performance of activities nor causes sedation. No harmful effects in such activities are expected based on ondansetron pharmacology.

3. HOW TO TAKE ONDANSETRON VIANEX

Always take Ondansetron Vianex exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Ondansetron Vianex solution for injection is administered intramuscularly or intravenously.

Chemotherapy and Radiotherapy induced Nausea and Vomiting:

Adults:
Ondansetron solution for injection dosage ranges from 8 to 32 mg daily and is selected as shown below.

Mild Emetogenic Chemotherapy and Radiotherapy:
For patients receiving emetogenic chemotherapy or radiotherapy, ondansetron can be used either orally (tablets or syrup) or rectally or by intravenous or intramuscular injection.

The recommended dose for oral administration is 8 mg 1-2 hours immediately before treatment.

The recommended dose of ondansetron suppositories is one suppository 16 mg 1-2 hours before treatment.

Ondansetron recommended intravenous or intramuscular dose is 8 mg by slow intravenous or intramuscular injection immediately before treatment.

To protect against delayed or prolonged vomiting after the first 24 hours, oral treatment with ondansetron 8 mg every 12 hours for up to 5 days should be continued or rectally with one ondansetron suppository 16 mg daily for up to 5 days.

Highly Emetogenic Chemotherapy:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be used either rectally or by intravenous or intramuscular injection.

The recommended dose for oral administration is 24 mg co-administered with 12 mg of dexamethasone sodium phosphate given orally, 1-2 hours prior to chemotherapy.

A single dose of ondansetron 8 mg can be administered by slow intravenous injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg every 2-4 hours or by continuous intravenous infusion of 1mg/hour for up to 24 hours.

Alternatively, a single dose of 32 mg by continuous intravenous infusion for not less than 15 minutes, 1-2 hours before treatment or rectally 1 suppository 16 mg, 1-2 hours before treatment.

Ondansetron doses higher than 8 mg and up to 32 mg are administered only intravenously, diluted in 50-100 ml of saline or other compatible infusion fluid and infused for not less than 15 minutes.

The selection of the dose regimen should be determined based on the severity of the expected emetogenic response.

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the administration of a single intravenous dose of dexamethasone sodium phosphate 20 mg before chemotherapy.

To protect against delayed or prolonged vomiting after the first 24 hours, oral treatment with ondansetron 8 mg every 12 hours for up to 5 days should be continued or rectally with recommended dose of one ondansetron suppository 16 mg daily for up to 5 days.

Paediatric Population:

Chemotherapy induced nausea and vomiting in children aged ≥ 6 months and adolescents
The dose for chemotherapy induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see section 2.4).

Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and infused intravenously over not less than 15 minutes.

There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged chemotherapy induced nausea and vomiting. 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/m^2. The 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 daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for chemotherapy - Children aged ≥ 6 months and adolescents

BSA	Day 1[1,2]	Day 2-6 [2]
< 0,6 m^2	5 mg/m^2 IV followed by 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0,6 m^2	5 mg/m^2 IV followed by 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs

[1] The intravenous dose must not exceed 8 mg.
[2] The total daily dose must not exceed adult dose of 32 mg.

Dosing by bodyweight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see section 2.4).

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0,15 mg/kg. The intravenous dose must not exceed 8 mg.
Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.
Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2).

Table 2: Weight-based dosing for chemotherapy - Children aged ≥ 6 months and adolescents

Weight	Day 1 [1,2]	Days 2-6[2]
≤ 10 kg	Up to 3 doses of 0,15 mg/kg every 4 hrs	2 mg syrup every 12 hrs
> 10 kg	Up to 3 doses of 0,15 mg/kg every 4 hrs	4 mg syrup or tablet every 12 hrs

[1] The intravenous dose must not exceed 8mg.
[2] The total daily dose must not exceed adult dose of 32 mg.

The use of ondansetron suppositories in children is not recommended.

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

Post – Operative Nausea and Vomiting:

Adults:

For the prevention of post-operative nausea and vomiting, ondansetron can be administered either orally (tablets or syrup) or by intravenous or intramuscular injection.

The recommended dose for oral administration is 16 mg one hour prior to anaesthesia or 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg every 8 hours.

Alternatively, ondansetron injection may be administered as a single dose of 4 mg by slow intravenous or intramuscular injection at induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by slow intravenous or intramuscular injection is recommended.

Paediatric population

Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents
For prevention of post-operative nausea and vomiting 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 or after induction of anaesthesia.

For the treatment of post-operative nausea and vomiting 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 0,1 mg/kg up to a maximum of 4 mg.

There are no data on the use of ondansetron in the treatment of post-operative nausea and vomiting in children below 2 years of age.

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting. Slow intravenous injection is recommended (not less than 15 minutes).

The use of suppositories in children is not recommended.

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.

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 8 mg intravenously or orally 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 and frequency of dosing are required.

If you take more Ondansetron Vianex than you should
There is limited experience with ondansetron overdose. In most cases the symptoms are similar to those reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.

There is no specific antidote for ondansetron, therefore, in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
In overdose with ondansetron, the use of ipecac is not indicated, since patients may not respond because of the anti-emetic action of ondansetron itself.

If you forget to take Ondansetron Vianex
If you forget a dose and you have nausea or vomiting, take another dose as soon as posible and then continue as before. If you forget a dose but you do not have nausea or vomiting, take the next dose according to posology.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ondansetron Vianex can cause side effects, although not everybody gets them.

The following side effects are listed below per 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).

Immune system disorders
Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders
Very common: Headache.
Uncommon: Epileptic seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia)[1].
Rare: Dizziness during rapid intravenous administration.

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

Cardiac disorders
Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Constipation.
Local burning sensation following suppository's administration.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests[3].

General disorders and administration site conditions
Common: Local reactions at the intravenous injection site.

[1] They have been observed without definitive evidence of persistent clinical sequelae
[2] The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

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

Paediatric population
The adverse event profile in children and adolescents was comparable to that seen in adults.

If you notice any side effects that you do not understand, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE ONDANSETRON VIANEX

Keep out of the reach and sight of children.

Do not use Ondansetron Vianex after the expiry date which is stated on the carton.

Ondansetron Vianex solution for injection should be stored at ≤ 25° C.

6. FURTHER INFORMATION

What Ondansetron Vianex contains

The active ingredient is 2 mg Ondansetron per ml.

The other ingredients are citric acid monohydrate, sodium citrate, sodium chloride and water for injection.

What Ondansetron Vianex looks like and contents of the pack

Carton containing 1 ampoule from amber transparent glass, in a plastic tray with a package insert.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation holder:
VIANEX S.A., Tatoiou str., 14671 Nea Erythrea, Greece, Tel.: +30.210.8009111

Manufacturer:
VIANEX S.A. – PLANT A', 12thkm Athens-Lamia National Road, 14451 Metamorphossi, Attiki, Greece

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Information for the Healthcare Professional

Ondansetron Vianex solution for injection should not be administered in the same syringe or by infusion with any other medication.

Ondansetron Vianex solution for injection should be mixed only with the recommended infusion solutions.

Ondansetron Vianex injection ampoules should not be autoclaved.

Compatibility with intravenous fluids:
Ondansetron Vianex solution for injection should be mixed only with the recommended infusion solutions. In accordance with the good pharmaceutical practice, intravenous solutions should be

prepared at the time of infusion. However, it has been demonstrated that Ondansetron Vianex solution for injection is stable for seven days at room temperature (below 25ºC) under fluorescent light or in refrigerator with the following intravenous solutions for infusion:

- Sodium chloride 0,9% w/v for intravenous infusion
- Glucose 5% w/v for intravenous infusion
- Mannitol 10% w/v for intravenous infusion
- Ringer solution for intravenous infusion
- Potassium chloride 0,3% w/v and sodium chloride 0,9% w/v for intravenous infusion
- Potassium chloride 0,3% w/v and Glucose 5% w/v for intravenous infusion

Compatibility studies for ondansetron have been performed in polyvinylchloride infusion bags and administration sets. Adequate stability would also be conferred using polyethylene infusion bags or Type I glass bottles.
Ondansetron solutions in sodium chloride 0,9% w/v or glucose 5% w/v have been demonstrated to be stable in polypropylene syringes.

It is considered that ondansetron solution for injection when mixed with other compatible infusion fluids is stable in polypropylene syringes.

Note: The product should be maintained under appropriate aseptic conditions when prolongation of storage time is required.

Compatibility with other drugs: Ondansetron Vianex can be administered by intravenous infusion at 1mg/hour, from an infusion bag or infusion pump. The following drugs can be administered concomitantly with Ondansetron Vianex via a Y-type administration set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively):

Cisplatin:
Concentrations up to 0,48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

5-Fluorouracil:
Concentrations up to 0,8 mg/ml (e.g. 2,4 g in 3 litres or 400 mg in 500 ml) are administered at a rate of at least 20 ml per hour (500 ml per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of Ondansetron Vianex. The 5-fluorouracil infusion may contain up to 0,045% w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations ranging from 0,18 mg/ml to 9,9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), are administered over 10 minutes to one hour.

Etoposide:
Concentrations ranging from 0,14 mg/ml to 0,25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre) are administered over 30 minutes to 1 hour.

Ceftazidime:
Doses ranging from 250 mg to 2000 mg diluted in distilled water for injection, as recommended by the manufacturer (e.g. 2,5 ml for 250 mg and 10 ml for 2 g ceftazidime), and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide:
Doses ranging from 100 mg to 1 g diluted in distilled water for injection with 100 mg/5 ml cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:

Doses ranging from 10-100 mg diluted in distilled water for injection with 10 mg/5 ml doxorubicin, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone:
Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via a Y-type infusion set in combination with 8 or 32 mg ondansetron diluted in 50 - 100 ml of a compatible infusion fluid over approximately 15 minutes.

Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated via the administration of the two drugs through the same administration set in concentration of 32 mcg – 2,5 mg/ml for dexamethasone sodium phosphate and 8 mcg – 1 mg/ml for ondansetron.