Package Leaflet: Information for the user

ZOPHRALEN Solution for Injection 4 mg/2 ml
ZOPHRALEN Solution for Injection 8 mg/4 ml

Ondansetron

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is ZOPHRALEN Solution for Injection *In the rest of this leaflet ZOPHRALEN Solution for Injection is called ZOPHRALEN.*

What is in this leaflet

1. What ZOPHRALEN is and what it is used for

ZOPHRALEN belongs to a group of medicines called an anti-emetics. Some medicinal products or medical treatments may lead to the release of a substance that can cause nausea and vomiting.

ZOPHRALEN prevents the action of this substance and thus prevents nausea or vomiting.

Adults: ZOPHRALEN is indicated for the treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. ZOPHRALEN is also indicated for the prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric population: ZOPHRALEN is indicated for the treatment of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months and for the prevention and treatment of PONV in children aged ≥1 month.

2. What you need to know before you take ZOPHRALEN

Do not take ZOPHRALEN
– In case of allergy (hypersensitivity) to ondansetron or any other ingredient of ZOPHRALEN.
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

Respiratory adverse effects should be treated symptomatically and clinicians should pay particular attention to them, because they can be precursors of hypersensitivity reactions.

Rarely, transient ECG changes, including QT interval prolongation, have been reported in patients receiving ondansetron. Moreover, cases of torsade tachycardia (Torsade de Pointes) have been reported post-marketing, in patients using ondansetron. ZOPHRALEN should be administered with caution to patients who have or may develop QT prolongation. These cases include patients with electrolyte disorders, congenital prolonged QT syndrome or patients receiving medicinal products known to cause QT prolongation.

As Ondansetron is known to increase colon transit time, patients with signs of subacute intestinal obstruction, should be monitored after its administration.

In patients who have undergone an adenotonsillar surgery, prevention of nausea and vomiting with ZOPHRALEN, may mask occult bleeding. Therefore, such patients should be carefully monitored after administration of ondansetron.

Paediatric population: Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

Taking other medicines
You are kindly requested to inform your doctor or pharmacist about any medicines you may be taking or have recently been taking, even those that were not prescribed.

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, frusemide, 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, rifampicin), the oral clearance of ondansetron was increased and ondansetron concentrations in blood were decreased.

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

Use of ZOPHRALEN with QT prolonging drugs may result in additional QT prolongation. Coadministration of ZOPHRALEN with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmia.

Pregnancy and breastfeeding
The safety of ondansetron use, during 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 foetus, the course of pregnacy and peri- and post-natal development. However, as animal studies are not always predictive of human response, the use of ondansetron during pregnancy is not recommended.

Tests have shown that ondansetron passes into the milk of lactating animals. Therefore, it is recommended that mothers receiving ondansetron should not breast-feed their infants.

Driving and using machines
In psychomotor testing, ondansetron does not impair performance nor cause sedation. According to the pharmacology of ondansetron, harmful effects in such activities are not anticipated.

Important information about some of the ingredients of ZOPHRALEN
None.

3. How to take ZOPHRALEN

You should always take ZOPHRALEN, strictly, according to the instructions of your doctor. If in doubt, ask your doctor or pharmacist.

ZOPHRALEN Solution for Injection is administered intravenously or intramuscularly.

Nausea and vomiting associated with chemotherapy and radiotherapy:

Adults:
ZOPHRALEN dose ranging from 8 mg to 32 mg per day and is selected as described below.

Mild emetogenic chemotherapy and radiotherapy:
For patients receiving emetogenic chemotherapy or radiotherapy, ZOPHRALEN can be given either by intravenous or intramuscular injection.

The recommended dose of ZOPHRALEN is 8 mg and it is administered by a slow intravenous or intramuscular injection right before treatment.

For protection against delayed or prolonged emesis after the first 24 hours, ondansetron treatment must be continued with oral administration of 8 mg per 12 hours for up to 5 day.

Highly emetogenic chemotherapy:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ZOPHRALEN can be given either intravenously or intramuscularly.

A single dose of 8mg of ZOPHRALEN may be administered by slow intravenous injection right before the chemotherapy, followed by either 8 mg every 2-4 hours for 2 more intravenous or intramuscular doses or by continuous intravenous infusion of 1mg/h for up to 24 hours.

Alternatively, 32 mg of ZOPHRALEN may be administered by intravenous infusion in a time range of at least 15 minutes, 1-2 hours before the therapy.

Doses higher than 8mg and up to 32mg are administered only intravenously, diluted to 50 – 100 mL of saline or other compatible infusion fluid in not less than 15 minutes.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.
The efficacy of ZOPHRALEN in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of 20 mg of dexamethasone sodium phosphate, prior to chemotherapy.

For protection against delayed or prolonged emesis after the first 24 hours, ondansetron treatment must be continued with oral administration, with the therapeutic regimen of 8 mg every 12 hours for up to 5 days.

Paediatric population:

CINV in children aged ≥ 6 months and in adolescents:

The dose for CINV 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).
ZOPHRALEN should be diluted to 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and injected intravenously for at least 15 minutes.

There are no data from controlled clinical trials on the use of ZOPHRALEN in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of ZOPHRALEN for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:
ZOPHRALEN should be administered right before chemotherapy as a single intravenous dose of 5 mg/m^2. The intravenous dose must not exceed 8 mg.
Oral dosing can commence 12 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[(a,b)]	Days 2 – 6[(b)]
$< 0.6\ m^2$	5 mg/m^2 IV followed by 2 mg syrup after 12 hours	2 mg syrup every 12 hours
$\geq 0.6\ m^2$	5 mg/m^2 IV followed by 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours

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

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

ZOPHRALEN should be administered right before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg.
Two more intravenous doses may be given in 4-hour intervals. The total daily dose must not exceed adult dose of 32 mg.

Oral dosing can commence 12 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

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

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

Elderly patients:
ZOPHRALEN is well tolerated by patients over 65 years of age, hence no alteration in dosage, dosage frequency and route of administration, is required.

Post-operative nausea and vomiting (PONV):
Adults:
For the prevention of PONV ZOPHRALEN can be administered by intravenous or intramuscular injection.

ZOPHRALEN may be administered as a single dose of 4 mg by slow intravenous or intramuscular injection during anaesthesia induction.
For the treatment of established PONV, a single dose of 4 mg, by slow intravenous or intramuscular injection, is recommended.

Paediatric population:

PONV in children aged ≥ 1 month and adolescents:
For the prevention of PONV in paediatric patients who have undergone a surgery under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (for over at least 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to or after anaesthesia induction.

For the treatment of PONV in paediatric patients who have undergone a surgery under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (for over at least 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 ZOPHRALEN in the treatment of PONV in children below 2 years of age.
There are no studies on oral administration of ondansetron for prevention or treatment of PONV. Slow intravenous injection is recomended (for at least 15 minutes).

Elderly patients:
There is limited experience in the use of ZOPHRALEN in the prevention and treatment of PONV in elderly patients, however, ZOPHRALEN is well tolerated by patients over 65 years of age receiving chemotherapy.

Patients with renal impairment:
No alteration in daily dosage, dosage frequency and route of administration, is required.

Patients with hepatic impairment:
Clearance of ZOPHRALEN is significantly reduced and half-life in blood serum is significantly prolonged, in subjects with moderate or severe impairment of hepatic function. In such patients the total daily dose should not exceed 8 mg, either intravenously or orally.

Patients with poor sparteine/debrisoquine metabolism:
The half-life of ondansetron is not altered, in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients, repeated doses achieve the same levels, in blood serum, as those of the general population. No alteration in daily dosage and dosage frequency, is required.

If you take higher than the normal ZOPHRALEN dose
There is limited experience with ondansetron overdose. In the majority of cases, the side effects were similar to those already reported in patients receiving recommended doses. Effects, that have been reported include, visual disturbances, severe constipation, hypotension and vasovagal episode with transient second degree AV block. There is no specific antidote to ondansetron, therefore, in cases of suspected overdose there should be symptomatic and supportive treatment. The use of ipecacuanha, to treat ondansetron overdose, is not recommended, as patients are not likely to respond, due to the very anti-emetic action of ZOPHRALEN itself.

If you miss a ZOPHRALEN dose
If you miss a dose and you have nausea or vomiting, take another dose as soon as possible and then continue as instructed. If you miss a dose but you do not have nausea or vomiting, take the next dose according to dosage.

4. Possible side effects

Like all medicines, ZOPHRALEN may cause side effects, although not everybody gets them.

Adverse effects are listed below by system organ class and frequency. Frequencies are defined as: 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) and very rare (<1/10,000).

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)[1].
Rare: Dizziness during rapid intravenous administration.

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

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

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 hepatic function tests[3].

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

[1] Have been observed without definitive evidence of persistent clinical sequelae.
[2] The majority of reported blindness cases were 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 commonly observed in patients receiving chemotherapy with cisplatin.

<u>Paediatric population</u>
The adverse effects profile in children and adolescents were comparable to that seen in adults.

If you experience other symptoms, that you do not understand, inform your doctor or pharmacist.

5. How to store ZOPHRALEN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

6. Contents of the pack and other information

What ZOPHRALEN contains
The active substance is 2 mg of ondansetron per 1 mL
The other ingredients are citric acid monohydrate, sodium citrate dihydrate, sodium chloride and water for injections.

What ZOPHRALEN looks like and contents of the pack
ZOPHRALEN is a clear, colourless solution for injection which can be diluted before use.
Each plastic or glass ampoule will contain 2 mL or 4 mL of your medicine.

Marketing Authorisation Holder and Manufacturer:
Demo S.A. Pharmaceutical Industry, 21st km National Road Athens – Lamia,
145 68 Krioneri Attica, Greece.

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PACKAGE LEAFLET: INFORMATION FOR THE PHYSICIAN

ZOPHRALEN should not be administered in the same syringe or by drip infusion with any other medication.
ZOPHRALEN should be admixed only with the recommended, for intravenous infusion, fluids.
ZOPHRALEN ampoules should not be placed in autoclave.

Instructions on the correct way of opening the ampoule.

Compatibility with intravenous fluids:

ZOPHRALEN should be admixed only with the recommended, for intravenous infusion, fluids. In order to be in compliance with good pharmaceutical practice, intravenous solutions should be prepared at the time of the infusion. However, it has been demonstrated that ZOPHRALEN is stable for 7 days at room temperature (below 25°C) with fluorescent lighting or in a refrigerator with the following intravenous fluids used for infusion:

- Sodium chloride 0.9% w/v solution for intravenous infusion.
- Glucose 5% w/v solution for intravenous infusion.
- Mannitol 10% w/v solution for intravenous infusion.
- Ringer's solution for intravenous infusion.
- Potassium chloride 0.3% w/v and sodium chloride 0.9% w/v solution for intravenous infusion.
- Potassium chloride 0.3% w/v and glucose 5% w/v solution for intravenous infusion.

Compatibility studies, of ZOPHRALEN with PVC bags and devices used for infusion, have been performed. Satisfactory stability also provided by using polyethylene bags or Type I glass ampoules. ZOPHRALEN solutions, in sodium chloride 0.9% w/v or glucose 5% w/v, are stable in polypropylene syringes.
ZOPHRALEN is considered stable in polypropylene syringes, when admixed with other compatible infusion fluids.
Note: The product should be kept in appropriate aseptic conditions, when the extension of its shelf life is required.

Compatibility with other drugs:
ZOPHRALEN can be administered by intravenous infusion at 1 mg/h, via an infusion bag or pump. The following drugs may be administered along with ZOPHRALEN via the Y-site of an infusion set for ondansetron concentrations of 16 – 160 mcg/mL (e.g. 8 mg/500 mL & 8 mg/50mL respectively):

Cisplatin:
Concentrations up to 0.48 mg/mL (e.g. 240 mg/500 mL), administered for over 1 – 8 hours.

5-Fluorouracil:
Concentrations up to 0.8 mg/mL (e.g. 2.4 g/3 L or 400 mg/500 mL), are administered at a rate of at least 20 mL/h (500mL/24h) Higher concentrations of 5-fluorouracil may cause precipitation of ZOPHRALEN. The 5-fluorouracil infusion may include magnesium chloride up to 0.045% w/v along with other compatible excipients.

Carboplatin:
Concentrations ranging from 0.18 mg/mL to 9.9 mg/mL (e.g. from 90 mg/500 mL to 990 mg/100 mL), are administered for a period of 10 minutes to 1 hour.

Etoposide:
Concentrations ranging from 0.14 mg/mL to 0.25 mg/mL (e.g. from 72 mg/500 mL to 250 mg/L), are administered over for a period of 30 minutes to 1 hour.

Ceftazidime:
Doses ranging from 250 mg to 2000 mg are reconstituted with bis-distilled water for injection according to the manufacturer's instructions (e.g. 2.5 mL for 250 mg and 10 mL for 2 g of ceftazidime) and administered by an intravenous injection for about 5 minutes.

Cyclophosphamide:
Doses ranging from 100 mg to 1 g, are reconstituted with bis-distilled water for injection, 5 mL per 100 mg of cyclophosphamide, as recommended by the manufacturer and administered by an intravenous injection for about 5 minutes.

Doxorubicin:
Doses ranging from 10 mg to 100 mg, are reconstituted with bis-distilled water for injection, 5 mL per 10 mg of doxorubicin, as recommended by the manufacturer and administered by an intravenous injection for about 5 minutes.

Dexamethasone:
20 mg of dexamethasone sodium phosphate are administered by slow intravenous injection for over 2 – 5 minutes via the Y-site of an infusion set, together with 8 mg or 32 mg of ZOPHRALEN, diluted in 50 – 100 mL of a compatible infusion fluid and injected for about 15 minutes.

Compatibility between dexamethasone sodium phosphate and ZOPHRALEN has been demonstrated by the administration of these drugs through the same device in concentrations from 32 mcg/mL to 2.5 mg/mL of dexamethasone sodium phosphate and from 8 mcg/mL to 1 mg/mL of ZOPHRALEN.