Package Leaflet: Information for the User
Zofran® 4 mg/2 ml (or 8 mg/4 ml)
Solution for Injection or Infusion
ondansetron (as hydrochloride dihydrate)

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 about your illness or your medicine, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Zofran Solution for Injection or Infusion is and what it is used for

Zofran Solution for Injection or Infusion (called 'Zofran injection' in this leaflet) contains a medicine called ondansetron (as hydrochloride dihydrate). This belongs to a group of medicines called anti-emetics.

Zofran injection is used for:

- preventing nausea and vomiting caused by chemotherapy or radiotherapy for cancer in adults
- preventing and treating nausea and vomiting after surgery in adults
- preventing nausea and vomiting caused by chemotherapy for cancer in children and adolescents aged from 6 months to 17 years
- preventing and treating nausea and vomiting after surgery in children and adolescents aged 1 month to 17 years

Ask your doctor, nurse or pharmacist if you would like any further explanation about these uses.
Zofran injection should start to work soon after having the injection. You must talk to a doctor if you do not feel better or if you feel worse.

2. What you need to know before you have Zofran Solution for Injection or Infusion

Do not have Zofran injection if:

- if you are taking apomorphine (used to treat Parkinson's disease)
- you are allergic (hypersensitive) to ondansetron or any of the other ingredients in Zofran injection (listed in Section 6).

If you are not sure, talk to your doctor, nurse or pharmacist before having Zofran injection.

Warnings and precautions
Check with your doctor or pharmacist before having Zofran injection if:

- you have ever had heart problems
- you have an uneven heart beat (arrhythmias)
- you are allergic to medicines similar to ondansetron, such as granisetron (known as 'Kytril')
- 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 having Zofran injection.

Tell your doctor or pharmacist immediately if you get any of these symptoms during and after the treatment with ZOFRAN

- if you experience sudden chest pain or chest tightness (myocardial ischemia).

Other Medicines and Zofran

Please tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Zofran can affect the way some medicines work. Also some other medicines can affect the way Zofran 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, as these medicines may reduce the effect of Zofran
- rifampicin, used to treat infections such as tuberculosis (TB), as this medicine may reduce the effect of Zofran
- anti-arrhythmic medicines used to treat an uneven heart beat, as these medicines may interact with Zofran & effect the rhythm of the heart
- beta-blocker medicines used to treat certain heart or eye problems, anxiety or prevent migraines, as these medicines may interact with Zofran and effect the rhythm of the heart
- tramadol, a pain killer, as Zofran may reduce the effect of tramadol
- medicines that affect the heart (such as haloperidol or methadone)
- cancer medicines (especially anthracyclines), as these may interact with Zofran to cause heart arrhythmias
- medicines used to treat depression and/or anxiety:
    - ° SSRIs (selective serotonin reuptake inhibitors) including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram
    - ° SNRIs (serotonin noradrenaline reuptake inhibitors) 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 Zofran injection.

Zofran injection should not be given in the same syringe or infusion (drip) as any other medication.

Pregnancy, breast-feeding and fertility

You should not use Zofran during the first trimester of pregnancy. This is because Zofran can slightly increase the risk of a baby being born with cleft lip and/or cleft palate (openings or splits in the upper lip and/or the roof of the mouth). If you are already pregnant, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking Zofran. If you are a woman of childbearing potential you may be advised to use effective contraception.

Driving and using machines
Zofran is not expected to impair the ability to drive. However, if any of the side effects (listed section 4) affect you (e.g. dizziness, blurred vision) caution is advisable. **Do not drive or operate machines if you are feeling unwell.**

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially "sodium free". If your doctor uses a solution of common salt to dilute Zofran, the dose of sodium received would be larger.

3. How to have Zofran Solution for Injection or Infusion

Zofran injection is normally given by a nurse or doctor. The dose you have been prescribed will depend on the treatment you are having.

To prevent nausea and vomiting from chemotherapy or radiotherapy

Adults:
On the day of chemotherapy or radiotherapy

- A single dose should not be more than 16mg.
- the usual adult dose is 8 mg given by an injection into your vein over at least 30 seconds or muscle, just before your treatment, and possibly another two 8 mg doses given by injection into your vein over at least 30 seconds or muscle four hours apart, depending on the strength of your chemotherapy or radiotherapy. After chemotherapy, your medicine will usually be given by mouth as an 8 mg Zofran tablet or 10 ml (8 mg) Zofran syrup.

On the following days
- the usual adult dose is one 8 mg tablet or 10 ml (8 mg) syrup taken twice a day
- this may be given for up to 5 days.

If your chemotherapy or radiotherapy is likely to cause severe nausea and vomiting, you may be given more than the usual dose of Zofran. Your doctor will decide this.

Elderly:
If you are over 65 years of age, your doctor will adjust your dose as required.

Children and Adolescents (aged 6 months to 17 years): To prevent nausea and vomiting from chemotherapy only

The doctor will decide the dose. Look at the label for more information

On the day of chemotherapy

- the first dose is given by an injection into the vein (up to 8mg), just before your child's treatment. After chemotherapy, 12 hours after the initial injection, your child's medicine will usually be given by mouth; -in tablet format up to 4mg twice a day or 5 ml (4 mg) Zofran syrup.

On the following days

- Up to one 4 mg tablet or 5 ml (4 mg) syrup every twelve hours
- This can be given for up to five days.

To prevent nausea and vomiting after an operation

- The usual dose for adults is 4 mg given by an injection into your vein or muscle. This will be given just before your operation.

- For children aged 2 years and over, the doctor will decide the dose. The maximum dose is 4 mg given as an injection into the vein. This will be given just before the operation.

To treat nausea and vomiting after an operation
- The usual adult dose is 4 mg given by an injection into your vein or muscle.
- For children aged 2 years and over, the doctor will decide the dose. The maximum dose is 4 mg given as an injection into the vein.

Patients with moderate or severe liver problems

The total daily dose should not be more than 8 mg. If you have blood tests to check how your liver is working this medicine may affect the results.

If you have more Zofran injection than you should

Your doctor or nurse will give you or your child Zofran injection so it is unlikely that you or your child will receive too much. If you think you have been given too much or have missed a dose, tell your doctor or nurse.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious

STOP taking or receiving ZOFRAN and seek medical help immediately if you or your child experience any of the following:

Allergic reactions

These reactions are rare in people taking Zofran. If you have an allergic reaction, tell your doctor or a member of the medical staff 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.

Myocardial ischemia: Signs include:
- sudden chest pain or
- chest tightness

Other possible side effects include the following listed below. If these side effects become severe, please tell your doctor, pharmacist or healthcare provider.

Very common (affects more than 1 in 10 people)
- headache.

Common (affects less than 1 in 10 people)
- a feeling of warmth or flushing
- constipation
- changes to liver function test results (if you have Zofran injection with a medicine called cisplatin, otherwise this side effect is uncommon)
- irritation and redness at the site of injection.

Uncommon (affects less than 1 in 100 people)
- hiccups
- low blood pressure, which can make you feel faint or dizzy
- uneven heart beat
- slow heart rate
- chest pain
- fits
- unusual body movements or shaking.

Rare (affects less than 1 in 1,000 people)
- feeling dizzy or light headed during IV administration
- blurred vision
- Disturbance in heart rhythm (sometimes causing a sudden loss of consciousness).

Very rare (affects less than 1 in 10,000 people)
- a widespread rash with blisters and skin peeling on much of the body surface (toxic epidermal necrolysis)
- poor vision or temporary loss of eyesight, which usually comes back within 20 minutes.

If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet.

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 via HPRA Pharmacovigilance, Website: www.hpra.ie.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zofran Solution for Injection or Infusion

- Keep out of the sight and reach of children.
- Do not use Zofran injection after the expiry date which is stated on the pack after 'Exp'. The expiry date refers to the last day of that month.
- Do not store Zofran injection above 30°C. Store in the original package in order to protect from light.
- Zofran injection is a clear colourless solution, do not use if it has any other appearance, e.g. appears cloudy
- When Zofran injection is diluted in intravenous fluids:
    - it must be stored at 2 – 8°C for not more than 24 hours
    - it does not need to be protected from light during infusion.

6. Contents of the pack and other information

What Zofran injection contains
- The active ingredient is ondansetron (as hydrochloride dihydrate) in a solution for injection or infusion which has a concentration of 2 mg in each ml.
  Each 2 ml Zofran injection ampoule contains ondansetron 4 mg/2 ml.
  Each 5 ml Zofran injection ampoule contains ondansetron 8 mg/4 ml.
- The other ingredients are citric acid monohydrate (E330), sodium citrate (E331), sodium chloride and Water for Injections.

What Zofran injection looks like and contents of the pack

Zofran 2mg/mL Solution for Injection is a clear colorless solution filled into 2 mL and 5 mL glass ampoules.

Zofran strength 4mg/2ml. Packed in boxes of 5 or 10 ampoules. The Ampoule size is 2ml

Zofran Strength 8mg/4mL. Packed in boxes of 5 or 8 ampoules. The Ampoule size is 5 mL

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Novartis Pharmaceuticals Ireland Limited, Vista Building, Elm Park, Merrion Road, Ballsbridge, Dublin 4, Ireland.

Manufacturer
Novartis Pharma GmbH, Roonstrase 25, D-90429 Nuremberg, Germany

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Package leaflet: Information for Healthcare Professionals
Zofran 4 mg/2 ml (or 8mg/4 ml)
Solution for injection or Infusion
ondansetron (as hydrochloride dihydrate)

Please refer to the Summary of Product Characteristics (SPC) for further details on this product.

Qualitative and Quantitative Composition

Zofran Solution for Injection or Infusion:

- 2ml glass ampoules each containing 4 mg/2 ml ondansetron (as hydrochloride dihydrate) in aqueous solution for intramuscular or intravenous administration.
- 5ml glass ampoules each containing 8 mg/4 ml ondansetron (as hydrochloride dihydrate) in aqueous solution for intravenous or intramuscular administration.

Pharmaceutical Form

Solution for injection or infusion
Clear, colourless solution

Posology and Method of Administration

Zofran is also available for oral and rectal use to allow the route of administration and dosing to be flexible.

Chemotherapy and Radiotherapy induced nausea and vomiting (CINV and RINV)
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.

CINV and RINV in Adults
The dose range of Zofran Solution for Injection or Infusion is 8 to 32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy:

For most patients receiving emetogenic chemotherapy or radiotherapy, Zofran 8mg should be administered as a slow intravenous injection (in not less than 30 seconds) or intramuscular injection, immediately before treatment, followed by 8mg orally twelve hourly

Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1 of the SPC).

- A single dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy.
- A dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injection (in not less than 30 seconds) or intramuscular doses of 8mg four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A maximum initial intravenous dose of 16mg diluted in 50–100ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of Zofran may be followed by two additional 8mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.

The efficacy of ondansetron 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.
Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours. The recommended oral dose is 8 mg to be taken twice daily.
The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Paediatric population
CINV in Children and Adolescents (aged 6 months to 17 years)

The dose of CINV can be calculated based on body surface area (BSA) or weight. Weight-based dosing results in higher total daily doses compared to BSA-based
dosing (section 4.4 and 5.1 of the prescribing information).
There are no data from controlled clinical trials on the use of Zofran in the prevention of chemotherapy-induced delayed or prolonged nausea and vomiting. There are
no data from controlled clinical trials on the use of Zofran for radiotherapy-induced nausea and vomiting in children.
In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid (see Instructions for Use and
Handling) and infused over not less than 15 minutes.
Dosing by Body Surface Area (BSA)
Ondansetron should be administered immediately before chemotherapy as a single IV dose of 5 mg/m^2. The single IV 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 dose over 24 hours (given as divided doses) must not exceed adult
dose of 32 mg.

Table 1. BSA-based dosing for CINV (aged 6 months to 17 years)

BSA	**Day 1[a,b]**	**Days 2–6[b]**
< 0.6 m^2	5 mg/m^2 IV plus 2 mg syrup after 12 h	2 mg syrup every 12 h
> 0.6 m^2	5 mg/m^2 IV plus 4 mg syrup or tablet after 12 h	4 mg syrup or tablet every 12 h

a The intravenous dose must not exceed 8 mg
b the total dose over 24 hours 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 4.4 and 5.1 of the prescribing information).
Ondansetron should be administered immediately before chemotherapy as a single IV dose of 0.15 mg/kg. The single IV dose must not exceed 8 mg.
On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2).
The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Table 2. Weight-based dosing for CINV (aged 6 months to 17 years)

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

a The intravenous dose must not exceed 8 mg
b the total dose over 24 hours must not exceed adult dose of 32 mg

CINV and RINV in Elderly

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50–100ml of 0.9% Sodium Chloride
Injection or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.
In patients 75 years of age or older, the initial intravenous dose of Zofran should not exceed 8 mg. All intravenous doses should be diluted in 50–100 ml of 0.9%
Sodium Chloride Injection or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. The initial dose of 8 mg may be followed by two further
intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart (see section 5.2 of the SPC).

Post-Operative Nausea and Vomiting (PONV)

Adults
For the prevention of PONV the recommended dose of Zofran Solution for Injection or Infusion 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 intramuscular or slow intravenous injection is recommended.

Paediatric population – Children and Adolescents (aged 1 month to 17 years)
For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of Zofran may be administered by slow intravenous
injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.
For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of Zofran may be administered by
slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4 mg.
There are no data on the use of Zofran for the treatment of PONV in children under 2 years of age.

Elderly
There is limited experience in the use of Zofran in the prevention and treatment of PONV in the elderly, however Zofran 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 Zofran (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 IV or oral should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of Zofran (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.

Overdose
Symptoms and Signs
There is limited experience of Zofran overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses
(see section 4.8 *of the prescribing information*). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block. 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 Zofran, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.
The use of ipecacuanha to treat overdose with Zofran is not recommended, as patients are unlikely to respond due to the anti-emetic action of Zofran itself.

Reconstitution and dilution of Zofran Solution for Injection or Infusion

Compatibility with intravenous fluids
Zofran Solution for injection or infusion should only be mixed with those infusion solutions which are recommended:
- Sodium Chloride Intravenous Infusion BP 0.9%w/v
- Glucose Intravenous Infusion BP 5%w/v
- Mannitol Intravenous Infusion BP 10%w/v
- Ringers Intravenous Infusion
- Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP
- Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

In keeping with good pharmaceutical practice dilutions of Zofran injection in intravenous fluids should be prepared at the time of infusion or stored at 2–8^{o}C for no more than 24 hours before the start of administration.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles.

Dilutions of Zofran in sodium chloride 0.9%w/v or in glucose (dextrose) 5%w/v have been demonstrated to be stable in polypropylene syringes. It is considered that

Zofran injection or infusion diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs

Zofran Solution for injection or infusion may be administered by intravenous infusion at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving 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) 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. 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 in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.
Etoposide: Concentrations in the range 0.144 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10–100 mg reconstituted with Water for Injections BP, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over 2–5 minutes via the Y-site of an infusion set delivering 8 to 16 mg of ondansetron diluted in 50–100 ml of the following infusion fluids:

- Sodium Chloride Intravenous Infusion BP 0.9% w/v
- Glucose Intravenous Infusion BP 5% w/v
- Sodium Chloride Intravenous Infusion 0.9% w/v and Glucose Intravenous Infusion BP 5% w/v

over approximately 15 minutes

Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram – 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 1mg/ml for ondansetron.

Zofran Solution for Injection or Infusion should not be administered in the same syringe of infusion as any other medication.

Shelf Life

- 36 months (unopened)
- 24 hours (dilutions stored 2 – 8°C)

Special Precautions for Storage

- Store in the original container to protect from light
- Do not store above 30°C

Dilutions of Zofran injection in compatible intravenous infusion fluids are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place.

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