B. PACKAGE LEAFLET

Package leaflet: Information for the user

[Ondansetron] 2 mg/ml, Solution for injection/infusion
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 or 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 of the side effects, , talk to your doctor , or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What [Ondansetron] is and what it is used for

Ondansetron belongs to a group of drugs called anti-emetics. Ondansetron inhibits the effect of the neuro-transmitter serotonin in the brain. Serotonin causes nausea and vomiting.

[Ondansetron] is used for
- preventing and treating nausea and vomiting caused by cytotoxic chemotherapy (CINV) and radiotherapy (adults and children aged ≥ 6 months)
- preventing and treating nausea and vomiting in patients following an operation (PONV)(in adults and children aged ≥ 1 month)

Your doctor may have prescribed [Ondansetron] for another use. Always follow your doctor's advice.

2. What you need to know before you are given [Ondansetron]

Do not use Ondansetron
- if you are allergic to ondansetron or any of the other ingredients of this medicine (listed in section 6)
- if you receive apomorphine (medicine used to treat Parkinson's disease)
- if you have previously experienced allergy to other drugs belonging to the group of serotonin antagonists (eg. granisetron, dolasetron). It is, in such case, possible that you are also allergic to [Ondansetron].

Warnings and precautions
Talk to your doctor or nurse before taking [Ondansetron]
- if you have a blockage of your intestines or constipation, as you will need to be closely monitored by your doctor.
- if you are going to have or recently have had your tonsils removed, because treatment with Ondansetron may hide symptoms of internal bleeding.
- if you have heart problems (with arrythmias or conduction disorders) and are being treated with other medication such as anesthetics, anti-arrythmics or beta-blockers at the same time, because or the limited experience hereby.
- if you need to pay attention to your sodium intake. However, [Ondansetron] has a low content of sodium (less than 1 mmol per ampoule).

- if it is for children below the age of 6 months or with a body surface of less than 0.6 m^2.
- if you have liver problems.
- if children or adolescents receive ondansetron together with drugs, that may have a harmful effect on the liver. Careful monitoring of the liver function is recommended.
- if you have problems with the levels of salts in your blood, such as potassium and magnesium.

Please tell your doctor or nurse if you need to have a blood or urine test that you are being treated with [Ondansetron].

Tell your doctor if any of the above warnings apply to you.

Other medicines and [Ondansetron]
Ondansetron may have an effect on other drugs or other drugs may have an effect on [Ondansetron].

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

You must tell your doctor that you are using [Ondansetron], if he/she starts treating you with the following medicine:
- Drugs for epilepsy (phenytoin, carbamazepin), which may reduce the effect of ondansetron.
- Antibiotics and antifungal medicines (e.g. rifampicin, erythromycin or ketoconazole), which may reduce the effect of ondansetron.
- Pain relieving medicine (tramadol), which effect may be reduced by ondansetron.
- Medicines inducing heart damage (e.g.anthracyclines or trastuzumab)
- Anti-arrhythmic medicines used to treat an uneven heart beat (e.g. amiodarone)
- Drugs which may result in QT prolongation (heart rhythm disorder)
- Beta-blocker medicines used to treat certain heart or eye problems, anxiety or prevent migraines (e.g. atenolol or timolol)
- Serotonergic drugs (medicines of the type SSRI or SNRI, used in the treatment of depressions))
- Apomorphine (medicine used to treat Parkinson's disease), since drastic reduction in blood pressure and loss of consciousness have been reported during concomitant use of [Ondansetron] with apomorphine.

Contact your doctor. It may be necessary to adjust the dose.

Using [Ondansetron] with food and drink
You may use [Ondansetron] independently of food and drinks.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy:
Use in pregnancy has not been established and is not recommended.
If it is absolutely necessary that ondansetron be given caution should be exercised when prescribing to pregnant women especially in the first trimester. Your doctor should evaluate the risk/benefit balance.

Breast-feeding:
Do not take [Ondansetron] if you are breast-feeding, because it is excreted into the milk.

Driving and using machines
[Ondansetron] does not affect the ability to use any tools or machines or the ability to drive safely in traffic.

[Ondansetron] contains sodium
[Ondansetron] solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium- free'.

3. How [Ondansetron] will be used

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.

Adults
Your doctor or hospital may chose to give you ondansetron as injections, infusions or tablets. The dose is individual.

Paediatric population
CINV in children aged ≥ 6 months and adolescents:
Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and infused into a vein over not less than 15 minutes. Ondansetron should be administered immediately before chemotherapy as a single dose of 5 mg/m^2 or 0.15 mg/kg. injected into a vein. Oral dosing can commence twelve hours later and may be continued for up to 5 days. The total daily dose must not exceed 32 mg.

PONV in children aged ≥ 1 month and adolescents:
For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow injection into a vein (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg 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 ondansetron may be administered by slow injection into a vein (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg.
There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

If you receive more Ondansetron than you should
Your doctor or nurse will give you or your child [Ondansetron] so it is unlikely that you or your child will receive too much. If you think you or your child have been given too much or have missed a dose, tell your doctor or nurse. The symptoms of overdose are disturbances of vision, severe constipation, low blood pressure and disturbances in heart beat rhythm.

4. Possible side effects

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

Serious, rare side effects (occur in between 1 and 10 of 10,000 patients treated).
Tell your doctor or nurse immediately if you experience any of the following:
- Swollen tongue and throat
- Difficulty breathing
- Collapse.

Very common side effects (occur in more than 1 of 10 patients treated):
Headache.

Common side effects (occur in between 1 and 10 of 100 patients treated):
A sensation of reddening and warmth. Constipation.. Hypersensitivity reactions at the injection site (local swelling, pain, redness, tissue hardening).

Uncommon side effects (occur in between 1 and 10 of 1.000 patients treated):
Seizures. Hiccups. Low blood pressure. Irregular heart beats, heart pain and slow pulse. Involuntary movements. Involuntary eye movements. Sometimes changes in liver function have been observed.

Rare side effects (occur in between 1 and 10 of 10.000 patients treated):

Nettle rash (urticaria). Dizziness, transient blurred vision predominantly during intravenous administration.
- Anaphylactic shock including collapse, swollen tongue and throat and trouble with breathing. Abnormally rapid heart rhythm called "Torsade des pointes". If any of these symptoms occur, immediately seek medical attention.

Very rare side effects (occur in less than 1 of 10.000 patients treated):
Transient blindness predominantly during intravenous administration. Most of these blindness cases were resolved within 20 minutes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [Ondansetron]

- Keep out of the sight and reach of children.
- Protect from light.
- Do not use [Ondansetron] after the expiry date which is stated on the ampoule and the carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Ondansetron] contains
The active substance in 1 ml solution for injection is 2 mg ondansetron as Ondansetron hydrochloride dehydrate. Each 2 ml ampoule contains 4 mg Ondansetron. Each 4 ml ampoule contains 8 mg Ondansetron. The other ingredients are Sodium chloride (0.15 mmol Na^+/ml); Citric acid monohydrate; Sodium citrate (0.0026mmol Na^+/ml); Water for injections.

What [Ondansetron] looks like and contents of the pack
[Ondansetron] 2 mg/ml, Solution for injection/infuion is a clear liquid in brown glass ampoules.
Every ampoule contains 2 ml or 4 ml solution. They are marketed in packs of 1ampoule, 5 ampoules or 5 x 5 ampoules respectively. Not all pack sizes may be marketed.

Marketing Authorisation Holder
<to be completed nationally>

Manufacturer
Pharmathen S.A
6. Dervenakion str., 15351 Pallini, Attikis
Greece

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

This medicinal product is authorised in the Member States of the EEA under the following names:

Denmark	Ondilia
Ireland	Ondansetron
Germany	Ondansetron Winthrop
United Kingdom	Ondansetron

This leaflet was last approved in

The following information is intended for medical or healthcare professionals only.

Instructions for use and handling

For injection:
For single use only. Any unused solution should be discarded.
The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

For infusion:
May be diluted with solution for infusion containing: Sodium chloride 9 mg/ml (0.9%), Glucose 50 mg/ml (5 %), Mannitol 100 mg/ml (10 %), Potassium chloride 3 mg/ml (0.3%) + Sodium chloride 9 mg/ml (0.9 %) and Potassium chloride 3 mg/ml (0.3%) + Glucose 50 mg/ml (5 %) as well as Ringer solution for infusion.

Should not be mixed with other pharmaceutical products.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user, and these should, if dilution has not been performed controlled and under validated aseptic conditions, normally not exceed 24 hours at 2-8°C.

Posology and method of administration

For intravenous injection or after dilution for intravenous infusion.

Chemotherapy and radiotherapy induced nausea and vomiting

Adults
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Ondansetron should be flexible and selected as shown below.

Emetogenic chemotherapy and radiotherapy
For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by oral or intravenous administration.
For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron should initially be administered intravenously immediately before treatment, followed by 8 mg orally twelve hourly.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy
Either 8 mg as a slow intravenous bolus injection or as a short-term infusion lasting 15 minutes immediately before chemotherapy. If this initial dose has insufficient effect it can be supplemented by either 8 mg (intravenous bolus or 15 minutes' infusion) every 4th hour, at most twice, or continuous infusion of 1 mg/hour for 24 hours.

A single intravenous dose of 16mg diluted in 50- 100ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1).

For management of highly emetogenic chemotherapy, a dose of 8 mg of ondansetron may be administered by slow IV in not less than 30 seconds immediately before chemotherapy, followed by 2 further IV doses of 8 mg 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours.

The effect of ondansetron may be enhanced by the simultaneous administration of 20 mg dexamethasone intravenously or an equally potent dose of other glucocorticoids for intravenous use.

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 sections 4.4.and 5.1.
There are no data from controlled clinical trials on the use of Ondansetron in the prevention of delayed or prolonged CINV. 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 - see Table 1 below. 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 i.v. 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥0.6 m^2	5 mg/m^2 i.v. 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet after 12 hrs

a The intravenous dose must not exceed 8mg.
b 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 sections 4.4. and 5.1).

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 (see Table 2 below).

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

Weight	**Day 1**[a,b]	**Days 2-6**[b]
≤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

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

Elderly

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section ‘’Instructions for use and handling’’) and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose of ondansetron should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section ''Instructions for use and handling'') 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. .

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 should not be exceeded and therefore parenteral or oral administration is recommended.

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 medicinal product exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

Post-operative nausea and vomiting (PONV)

Adults
For the prevention of PONV ondansetron can be administered orally or intramuscular or by slow intravenous injection at the induction of anesthesia.

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

For treatment of established PONV a single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population
Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents
For prevention of PONV 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 0.1mg/kg up to a maximum of 4mg 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 ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg.

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

Elderly
There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting (PONV) 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 should not be exceeded and therefore parenteral or oral administration is recommended.

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 medicinal product exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.