PATIENT INFORMATION LEAFLET

Osetron 8 mg/4 mL I.M./I.V. ampoule containing solution for injection

Administered by intramuscularly or intravenously.

- ***Active Ingredient:*** Contains 8 mg ondansetron (as hydrochloride dihydrate) in each ampoule (4 mL)
- ***Excipients:*** Citric acid monohydrate, sodium citrate, sodium chloride, water for injection

Read all of this LEAFLET carefully before you start using 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.*
- *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.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use high or low doses other than the recommended dosage.*

What is in this leaflet:

1. What OSETRON is and what it is used for?
2. What you need to know before you use OSETRON
3. How to use OSETRON?
4. Possible side effects
5. How to store OSETRON

1. What OSETRON is and what it is used for?

OSETRON contains ondansetron active ingredient. It is in ampoules each contains particle free, clear, colorless and odorless solution for injection and infusion.

OSETRON belongs to a group of medicines called anti-emetics. Some medications (e.g. cancer medications) may cause you to feel sick and vomit. OSETRON prevents you from feeling sick or vomiting.

Your doctor has chosen this drug according to you and your condition.

OSETRON is given to prevent you from feeling sick and vomiting after treatment.

2. What you need to know before you use OSETRON

DO NOT USE OSETRON

If ;

- You are allergic to Ondansetron or any of the other raw material in the OSETRON content.

Use OSETRON CAREFULLY if;

- You are hypersensitive (allergic) to other selective 5-HT3 receptor antagonists such as Granisetron (a group of drugs that prevent nausea and vomiting)
- You have complaints of intestinal obstruction or severe constipation
- You are pregnant or intending to become pregnant soon
- You are breastfeeding
- You have liver disease
- You have heart problems involving heartbeat irregularity (arrhythmia)

If these warnings are valid for you, even at any time in the past, please consult your doctor.

Use of OSETRON with food and drink

No data available.

Pregnancy

Consult your doctor or pharmacist before using this medication.

If you notice that you are pregnant during treatment, consult your doctor or pharmacist.

Breast-feeding

Consult your doctor or pharmacist before using this medication.

Do not use OSETRON when breast-feeding.

Driving and using machines

It is not likely to have any effect.

Important information about some of the excipients in OSETRON

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; however, no adverse side effects are expected for this dose.

Other medicines and OSETRON

If you use any drug product which contains phenytoin, carbamazepine and rifampicin as drug substance, the effect of OSETRON may be reduced.

If you use any drug product that contains tramadol as drug substance, OSETRON can reduce the pain relief effect of this drug product.

If you are taking medication with side effects on heart, the risk of developing heartbeat disorder (arrhythmia) may increase.

Please inform your doctor or pharmacist if you are currently using any prescription or non-prescription medication or if you have recently used it.

3. How to use OSETRON

Instructions for proper use and dosage / administration frequency:

Depending on your condition, your physician will determine the dose of your medicine and administer it to you.

Method of administration

Administered by intramuscularly or by intravenously.

Different age groups

Use in children :

Vomiting after chemotherapy and radiotherapy (from 6 months to 17 years):

The physician will determine the dose of the drug product depending on condition and administer it to your child.

Postoperative nausea and vomiting:

The physician will determine the dose of the drug product depending on condition and administer it to your child.

Use in the elderly:

In patients over 65 years, there is no need for changing the dose, frequency and route of administration of OSETRON.

Special cases for use:

Renal failure:

For renal failure there is no need for changing the dose, frequency and route of administration of OSETRON.

Liver failure:

In patients with moderate or severe liver dysfunction, the total daily dose of OSETRON should not exceed 8 mg.

If you have an impression that the effect of OSETRON is too strong or too weak, consult to your physician or pharmacist.

If you use more OSETRON than you should

Consult to a physician or pharmacist if you have used more OSETRON than you should use.

If you forget to use OSETRON

Do not use a double dose to make up for a forgotten dose.

Side effects after concluding treatment with OSETRON

Your doctor will administer OSETRON to you during the period of treatment.

4. Possible side effects

Like all medicines, OSETRON may have side effects in people who are sensitive to substances in its content.
This drug product did not cause any problems in the majority of patients who used this medicine.

If you have any of the following, stop using OSETRON and IMMEDIATELY tell your doctor or contact the emergency department of your nearest hospital:

- Hypersensitivity reactions. Symptoms;
  - Sudden snarls and jaw pain or jaw tension.
  - Swelling of the eyelids, face, lips, mouth or tongue.
  - Tuberous skin rash or urticaria anywhere in the body.

These are all very serious side effects.

If you have one of these, you have a serious allergy to OSETRON. You may need immediate medical attention or hospitalization.

Other side effects are classified as shown in the following categories:

Very common	: Can be seen in at least one of 10 patients.
Common	: Less than one in 10 patients, but more than one in 100 patients.
Uncommon	: Less than one in 100 patients, but more than one in 1,000 patients.
Rare	: Less than one in 1,000 patients.
Very rare	: Less than one in 10,000 patients.
Unknown	: Cannot be estimated from the data available.

Very common side effects:
- Headache

Common side effects:
- Fever or feeling hot flashes
- Constipation
- If you are taking it with a drug called cisplatin, there may be changes in your tests that show liver function, otherwise it is a non-common side effect.

Uncommon side effects:
- Hiccups
- Low blood pressure, asthenia
- Slow or irregular heart beats
- Chest pain
- Seizures

• Normal movements or swaying in the body
• Change in tests showing liver function

Rare side effects:
• Dizziness or lightheadedness
• Blurred vision
• Heart rhythm deterioration (sometimes can cause sudden loss of consciousness.)

Very rare side effects:
• Decreased vision or general vision loss of temporary vision in 20 minutes

If you encounter any side effects not mentioned in this patient information leaflet, please inform your doctor or pharmacist.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store OSETRON

Keep OSETRON out of the reach and sight of children and in its original package.

Store at room temperature below 25°C.

The prepared solution should be used immediately.

Use in accordance with the expiry date.

Do not use this medicine after the expiry date which is stated on the package.

Marketing Authorization Holder:

HAVER FARMA İlaç A.Ş.
Akbaba Mahallesi Maraş Cad. No: 52/2/1
Beykoz / İstanbul

Manufacturing Site:

Osel İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Cad. No:52
34820 Beykoz / İSTANBUL

This patient information leaflet approved in 28/05/2015 .

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Osetron 8 mg/4 mL I.M./ I.V. ampoule containing solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Each 4 mL ampoule;

Ondansetron (as hydrochloride dihydrate)…….8 mg

Excipients:

Sodium citrate…….1.0 mg

Sodium chloride…….36.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Particle free, clear, colorless and odorless solution for injection or infusion

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

OSETRON is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. OSETRON is also indicated for the prevention and treatment of post-operative nausea and vomiting.

4.2. Posology and method of administration

Posology /administrationfrequency and duration

Chemotherapy and Radiotherapy induced nausea and vomiting: Emetogenic potential of cancer treatment depends on the doses of chemotherapy combinations applied and the radiotherapy regimens used. OSETRON is also available in oral tablet forms which provide application and dosage flexibility. In adults with chemotherapy-induced nausea and vomiting, a low IV dose regimen (0.15 mg / kg three times at 4-hour intervals) may be used. However, the dose of single dose IV ondansetron should not exceed 16 mg due to the risk of QT prolongation.

Emmetogenic chemotherapy and radiotherapy: OSETRON can be given by oral or intravenous injection in patients receiving emmetogenic chemotherapy and radiotherapy. A low IV dose regimen (0.15 mg / kg three times at 4 hour intervals) can be used; It is slow intravenous injection just before treatment, but not less than 30 seconds. However, the dose of single dose IV ondansetron should not exceed 16 mg due to the risk of QT prolongation. Oral OSETRON treatment is recommended following the first day of treatment to avoid delayed or prolonged emesis after the first 24 hours.
Highly emetogenic chemotherapy: Patients undergoing high emetogenic chemotherapy, such as high doses of cisplatin, may be used with a low IV dose regimen (0.15 mg / kg three times at 4 hour intervals) immediately before OSETRON chemotherapy. However, the dose of single dose IV ondansetron should not exceed 16 mg due to the risk of QT prolongation. If doses greater than 8 mg are to be given, it should be diluted with 50-100 mL of saline or other infusion fluids and should be given as infusion in not less than 15 minutes.

For administration of highly emetogenic chemotherapy, intravenous injection of 8 mg administered less than 30 seconds not less than chemotherapy or two 8 mg intravenous doses with an interval of 2 to 4 hours following intramuscular injection or up to 24 hours 1 mg/hour continuous infusion. The choice of dosing regimen should be based on the therapeutic potential of the treatment administered (the severity of vomiting and nausea). In extremely emetogenic chemotherapy, the effect of OSETRON may be increased by the addition of a single dose of 20 mg of intravenous dexamethasone sodium phosphate prior to chemotherapy. Oral OSETRON treatment is recommended following the first day of treatment to avoid delayed or prolonged emesis after the first 24 hours.

Postoperative nausea and vomiting: In order to prevent post-operative nausea and vomiting, OSETRON may be given by oral, intramuscular or slow intravenous injection. The recommended dose of OSETRON injection is 4 mg intramuscular or slow intravenous injection in anesthesia induction. In the treatment of started post-operative nausea and vomiting, a single dose of 4 mg intramuscular or slow intravenous injection is administered.

Method of Administration:
Intramuscular or intravenous administration.

Additional information on special populations:
Renal impairment:

There is no need to change daily dosage, dosage frequency and route of administration.

Hepatic impairment:

In patients with moderate severe or severe liver dysfunction, ondansetron clearance is significantly reduced and serum half-life is significantly prolonged. In such patients, the total daily dose should not exceed 8 mg.

Pediatric population:

The dose for CINV (nausea and vomiting caused by cytotoxic chemotherapy - from 6 months to 17 years) can be calculated based on body surface area (BSA) or weight. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 mL of saline or other compatible infusion fluid and infused over not less than 15 minutes. Adult dose must not be exceeding.

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 dose can be initiated 12 hours later and may be continued for up to 5 days (Table 1). Adult doses should not be exceeded.

Table 1- CINV dose determination according to BSA (from 6 months to 17 years of age)

BSA	**1st Day**	**2-6th Days**
< 0.6 m^2	5 mg / m^2 i.v. + 12 hours later 2 mg syrup	2 mg syrup every 12 hours
≥ 0.6 m^2 and ≤ 1.2 m^2	5 mg / m^2 i.v. + 12 hours later 4 mg syrup or tablet	4 mg syrup or tablet every 12 hours
> 1.2 m^2	5 mg / m^2 i.v. or 8 mg i.v. + 12 hours after 8 mg syrup or tablet	8 mg syrup or tablet every 12 hours

Dosing by body weight

Ondansetron 0.15 mg/kg i.v. should be administered as a single dose just before chemotherapy. I.V. dose should not exceed 8 mg. On the first day, the dose can be given as 2 iv dose with 4 hours interval. Oral dose can be initiated 12 hours later and may be continued for up to 5 days (Table 2). Adult doses should not be exceeded.

Table 2. CINV dose determination based on body weight (from 6 months to 17 years)

Body weight	**1st Day**	**2-6th Days**
≤ 10 kg	Every four hours, up to 3 doses 0.15 mg / kg	2 mg syrup every 12 hours
> 10 kg	Every four hours, up to 3 doses 0.15 mg / kg	4 mg syrup or tablet every 12 hours

Postoperative nausea and vomiting (from 1 month to 17 years of age):

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

In surgical applications under general anesthesia to prevent post-operative nausea and vomiting in pediatric patients, ondansetron may be administered as a slow iv injection (not less than 30 seconds) up to a maximum of 4 mg at a dose of 0.1 mg/kg or before or after surgery.

Geriatric population:

Emmetogenic chemotherapy and radiotherapy:

Ondansetron is well tolerated in patients over 65 years of age and there is no need to change its dosage, dosage frequency and route of administration.

Postoperative nausea and vomiting:

There are limited studies on the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly. However, chemotherapy was well tolerated in patients over 65 years of age.

Other:

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 change in daily dosage is required.

Special preparation instructions

Ampoule formulations are not protected and have to be used only once, have to be injected or diluted immediately after opening, holded solutions have to be discarded.

Ampoules containing Ondansetron injection should not be autoclaved.

Compatibility with intravenous solutions: Ondansetron injection should be mixed with only recommended infusion solutions. In keeping with "good pharmaceutical practice" dilutions of Ondansetron injection in intravenous solutions should be prepared at the time of infusion. In addition, ondansetron injection has been shown to be stable for 7 days at room temperature (below 25 °C), under fluorescent light, or in a cooler with the following intravenous infusion solutions:

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 0.2% w/v and Glucose 5% w/v Intravenous Infusion BP.

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 Ondansetron in sodium chloride 0.9%w/v or in glucose 5%w/v have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron injection diluted with other compatible infusion solutions would be stable in polypropylene syringes.

Note: If it is desired to store injectable mixtures of infusion solutions with OSETRON for a long time after preparation, mixing should be carried out under appropriate aseptic conditions.

Compatibility with other drugs: Ondansetron may be administered by intravenous infusion at 1 mg/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 2 g 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 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16 mg of 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 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 – 1 mg/mL for ondansetron.

Ampoule opening instructions

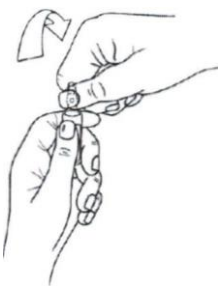
The ampoules are equipped with OPC (One Point Cut) opening system and must be opened according to the following instructions:

• Hold the ampoule at the bottom as shown in figure 1.

• Press on the top of the ring line on the ampoule with the thumb of the other hand as shown in Figure 2.

Figure 1

Figure 2



4.3. Contraindications

Should not be used in case of hypersensitivity to any of the substances in the composition of the drug product.

Concomitant use of ondansetron with apomorphine hydrochloride is contraindicated due to severe hypotension and loss of consciousness.

4.4. Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists.

Ondansetron prolongs the QT interval in a dose-dependent manner (see Clinical Pharmacology). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to 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.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

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

In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

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

Contains less than 1 mmol sodium (23 mg) per 2 mL; no side effects related to sodium is expected in that dose.

4.5. Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either 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, tramadol and propofol pharmacokinetically.

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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. (See section Special warnings and precautions for use)

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.

Apomorphine

Concomitant use of ondansetron with apomorphine hydrochloride is contraindicated due to reports of severe hypotension and loss of consciousness.

Tramadol

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

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

Additional information for special populations:

There is no information.

Pediatric population:

There is no information.

4.6 Pregnancy and lactation

General advice

Pregnancy category is B

Women with child-bearing potential / Contraception

Clinical data on exposure to ondansetron are not available.

Animal studies do not show any direct or indirect adverse effects on pregnancy/embryonal /fetal development/ birth or postnatal development.

Caution should be exercised when giving it to women with childbearing potential.

Pregnancy

The safety of ondansetron for use in 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 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.

Lactation

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 babies.

Fertility

There is no information.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable effects

Frequency class is as follows:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1000 and <1/100

Rare ≥1/10000 and < 1/1000

Very rare <1/10000

Unknown (It can not be estimated from the available data).

Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post- marketing spontaneous data.

The following frequencies have been calculated at the standard recommended doses of ondansetron according to indication and formulation. The adverse event profiles in children and adolescents were comparable to that seen in adults.

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, ocular-toxic crises and dyskinesia without persistent clinical sequelae)
Rare:	Dizziness seen throughout iv administration (in many cases, the infusion time is extended or prevented)

Eye disorders

Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during rapid intravenous administration.
Very rare:	Transient blindness predominantly during rapid intravenous ondansetron 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.

Cardiac disorders

Uncommon:	Arrhythmias, chest pain (with or without ST segment depression) bradycardia.
Rare:	QTc prolongation (including Torsade de Pointes)

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 liver function tests

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

General disorders and administration site conditions

Common: Local I.V. injection site reactions.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms and Signs

There is limited experience of ondansetron overdose. In addition, two patients with intravenous 84 mg and 145 mg had side effects and no active treatment was required.

The symptoms in the majority of collars are similar to those reported in patients receiving the recommended doses (see Undesirable Effects).

Ondansetron prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.

Treatment

There is no specific antidote for ondansetron. When overdosing is suspected, appropriate symptomatic and supportive treatment should be performed.

The use of apomorphine and ipecacuanha to treat overdose with ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic grup: Selective $5HT_3$ receptor-antagonist

ATC code: A04AA01

Ondansetron; It is a potent, highly selective 5-HT3 receptor antagonist. The mechanism of action in controlling vomiting and nausea is not fully known.

Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5\text{-}HT_3$ receptors. Ondansetron blocks the initiation of this reflex.

Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on

the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5-HT_3 receptors on neurons located both in the peripheral and central nervous system.

The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.
Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, 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.

5.2 Pharmacokinetic properties

Absorption

Systemic exposure levels after intramuscular or intravenous administration of ondansetron are equivalent.

Distribution:

The disposition of ondansetron following oral, intramuscular and intravenous dosing in adults is similar. Steady state volume of distribution of about 140 L. A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/mL. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/mL are attained within 10 minutes of injection. Ondansetron is not highly protein bound (70-76%). Gender-related differences were observed in the ondansetron distribution. The distribution volume is lower in women.

Biotransformation:

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

Elimination:

Terminal elimination half life is about 3 hours. Less than 5% of the absorbed dose is excreted unchanged in the urine. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Characteristics of patients

Gender

Absorption is faster and more rapid in women following oral doses; systemic clearance and volume of distribution (adjusted for weight) is low.

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n = 19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n = 22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the 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.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children.

Clearance depends on weight but is not dependent on age, except in infants 1 to 4 months old.

It is difficult to conclude whether there is an additional reduction in clearance due to age in infants 1 to 4 months of age, or whether there is a natural variability due to the small number of individuals. Since patients younger than 6 months of age will only receive a single dose of ondansetron in PSNV (post-surgery nausea and vomiting), clinically relevant low clearance is unlikely.

Elderly

Studies on healthy elderly volunteers showed a mild age-related increase in oral bioavailability and half-life.

Renal impairment

Following iv administration of ondansetron in patients with moderate renal impairment (creatinine clearance 15-60 mL/min), a slight but clinically insignificant increase in elimination half-life (5.4 hours) occurs due to a reduction in both the volume of distribution and systemic clearance. In a study in patients with severe renal impairment requiring regular hemodialysis (studied between dialysis) i.v. The pharmacokinetics of ondansetron was essentially unchanged following administration.

Hepatic impairment

Following oral, intravenous or intramuscular dosing 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 pre-systemic metabolism.

5.3 Preclinical safety data

In one study of copied human cardiac ion channels, ondansetron has been shown to have a potential to affect cardiac repolarization by blocking hERG potassium channels at clinically relevant concentrations.

In 2 years of studies on rats and mice, carcinogenic effects were not observed with oral ondansetron doses of 10 mg/kg and 30 mg/kg, respectively. Ondansetron is not mutagenic according to standard tests of mutagenicity. Oral doses of ondansetron up to 15 mg / kg per day did not affect fertility or general reproductive performance in male and female rats.

Reproduction studies were performed at 15 mg/kg and 30 mg/kg oral doses per day in pregnant rats and rabbits, respectively, and there was no sign of impaired fertility or a deleterious effect on fetus due to ondansetron. However, since studies on animals do not always provide foresight, the use of ondansetron in pregnant women is not recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Sodium citrate

Sodium chloride

Water for injection

6.2 Incompatibilities

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

Ondansetron injection should only be mixed with those infusion solutions that are recommended.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep at room temperature below 25 ° C.

The prepared solution should be used immediately.

6.5 Nature and contents of container

4 mL x 1 piece amber type I glass ampoule in carton box

6.6 Special precautions for disposal

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

HAVER FARMA İlaç A.Ş.

Akbaba Mahallesi Maraş Cad.

No:52/2/1 Beykoz / İstanbul/TURKEY

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