Dr/Marwa 28/6/2022

Ondametic
4 mg/2 ml & 8 mg/4 ml
Solution For IM & Slow IV Injection or IV Infusion
(Ondansetron)

Name of the medicinal product
Ondametic

Qualitative and quantitative composition

Ondametic 4 mg/2 ml :
Each ampoule 2 ml contains:
Active ingredient:
Ondansetron hydrochloride dihydrate 4.988 mg equivalent to 4 mg ondansetron.
Inactive ingredient:
Sodium chloride, Citric acid anhydrous, Sodium citrate dihydrate and water for injection.

Ondametic 8 mg/4 ml :
Each ampoule 4 ml contains:
Active ingredient:
Ondansetron hydrochloride dihydrate 9.976 mg equivalent to 8 mg ondansetron.
Inactive ingredient:
Sodium chloride, Citric acid anhydrous, Sodium citrate dihydrate and water for injection.

Pharmaceutical form
Solution For IM & Slow IV Injection or IV Infusion.
Physical characters: clear colourless solution.

Clinical particulars
Therapeutic indications
Adults:
Ondametic is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondametic is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Ondametic is indicated for the management 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.

Posology and method of administration
Chemotherapy and Radiotherapy induced nausea and vomiting
Adults:

Central Administration for Pharmaceutical care Approval Date 28/6/2022 Revisor Dr MarwaMahmoud
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: last approved leaflet "Ondametic 17-5-2020" after warning addition

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 Ondametic should be flexible in the range of 8-32 mg a day and selected as shown below.
Emetogenic chemotherapy and radiotherapy: Ondansetron can be given either by oral, rectal or intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondametic 8 mg should be administered as a slow intravenous injection (in not less than 30 seconds) or intramuscular injection, immediately before treatment, followed by 8 mg orally twelve hourly.
To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment.
Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given either by oral, rectal, intravenous or intramuscular administration. Ondametic has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:
• A single dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy.
• A dose of 8 mg 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 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.
• A maximum initial intravenous dose of 16 mg diluted in 50-100 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of Ondametic may be followed by two additional 8 mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.
A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk.
The selection of dose regimen should be determined by the severity of the emetogenic challenge. The efficacy of Ondametic in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate 20 mg administered prior to chemotherapy.
To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment.
Paediatric Population:
CINV in children aged ≥ 6 months and adolescents
The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of compatible infusion fluid and infused over not less than 15 minutes.
Weight-based dosing results in higher total daily doses compared to BSA-based dosing.
Ondametic injection should be diluted in Sodium chloride 0.9%, 5% glucose, mannitol 10% & ringer's solution and infused intravenously over not less than 15 minutes.
There are no data from controlled clinical trials on the use of Ondametic in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of Ondametic for radiotherapy-induced nausea and vomiting in children.
Dosing by BSA:

Ondametic should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The single 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 dose over 24 hours (given as divided doses) 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 plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0.6 m^2 to ≤ 1.2 m^2	5 mg/m^2 IV plus 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs
> 1.2 m^2	5 mg/m^2 or 8 mg IV plus 8 mg syrup or tablet after 12 hours	8 mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8 mg.
b The total dose over 24 hours (given as divided doses) 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.
Ondametic should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The single intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals.
Oral dosing can commence 12 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 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 IV every 4 hrs	2 mg syrup every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hrs	4 mg syrup or tablet every 12 hrs

a The intravenous dose must not exceed 8 mg.
b The total dose over 24 hours (given as divided doses) 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 compatible infusion fluid and infused over 15 minutes.
In patients 75 years of age or older, the initial intravenous dose of Ondametic should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of compatible infusion fluid 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 drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.
Post-Operative Nausea and Vomiting (PONV):
Adults:
For the prevention of PONV: ondansetron can be administered orally or by intravenous or intramuscular injection.
Ondametic may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at 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:
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 Ondametic may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, 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 Ondametic may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg.
There are no data on the use of Ondametic in the treatment of PONV in children below 2 years of age.
Elderly:
There is limited experience in the use of Ondametic in the prevention and treatment of PONV in the elderly, however Ondametic 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 drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

Contraindications

- **The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was *adminisetred* with ondansetron.**

Hypersensitivity to any component of the preparation.

Special warnings and precautions for use

Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms appeared immediately after administration but recovered with prompt treatment. Therefore, caution should be exercised during and after administration of ondansetron.

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

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

Ondansetron prolongs the QT interval in a dose-dependent manner). 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.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is known to increase large bowel transit time, patients with signs of sub-acute intestinal obstruction should be monitored following administration.

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 Population:

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

CINV:

When calculating the dose on an mg/kg basis and administering three doses at 4-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicates similar efficacy for both regimens.

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, 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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities.

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias.

Serotonergic Drugs (e.g. SSRIs and SNRIs): There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs).

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

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

Fertility, pregnancy and lactation

Women of childbearing potential:

Women of childbearing potential should consider the use of contraception.

Pregnancy

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformation when administered during the first trimester of 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.

Breast-feeding

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondametic should not breast-feed their babies.

Ondansetron should not be used during the first trimester of pregnancy.

Fertility

There is no information on the effects of ondansetron on human fertility.

Effects on ability to drive and use machines

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

Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000). 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 are estimated at the standard recommended doses of ondansetron. 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, oculogyric crisis and dyskinesia) (1).

Rare: Dizziness predominantly during rapid IV administration.

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.

Very rare: Transient blindness predominantly during intravenous administration (2).

Cardiac disorders

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

Rare: QTc prolongation (including Torsade de Pointes).

Not known: Myocardial ischemia

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 (3).

General disorders and administration site conditions

Common: Local IV injection site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

The Egyptian Pharmacovigilance Center (EPVC): pv followup@edaegypt.gov.eg

1. Observed without definitive evidence of persistent clinical sequelae.
2. The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.
3. These events were observed commonly in patients receiving chemotherapy with cisplatin.

Overdose

Symptoms and Signs

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

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

Paediatric cases consistent with serotonin syndrome have been reported in young children following oral overdose of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

Treatment

There is no specific antidote for ondansetron, therefore, in all 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 ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

Pharmacological properties

Pharmacodynamic properties

Mechanism of Action

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 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 5HT3 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.
The role of ondansetron in opiate induced emesis is not yet established.

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. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Paediatric population

CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m2 intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m2 intravenous and ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous and placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m2 intravenous together with 2 to 4 mg dexamethasone orally
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for

children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. of children n = 22). Complete control of emesis was achieved in 42% of patients.

PONV

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≤44 weeks, weight ≥ 5 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (TT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p <0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg, number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3: Prevention and treatment of PONV in Paediatric Patients – Treatment response over 24 hours

Study	Endpoint	Ondansetron %	Placebo %	p value
S3A380	CR	62	39	<0.001
S3GT09	CR	61	35	<0.001
S3A381	CR	53	17	<0.001
S3GT11	no nausea	72	51	0.004
S3GT11	no emesis	69	47	0.004

CR = no emetic episodes, rescue or withdrawal

Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30 ng/mL are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional, this may reflect some reduction in first pass metabolism at higher oral doses. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron.

...disposition of ondansetron following oral, intramuscular and intravenous dosing in adults is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

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.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females showed small clinically insignificant, increase in half-life in comparison with males.

Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Special Patient Populations

Gender

Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

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 was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for IV dosing.

Renal Impairment

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following intravenous 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. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

Pharmaceutical particulars

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned below.

Shelf life
3 years

Special precautions for storage
Store at a temperature not exceeding 30°C. the diluted solution should be stored protected from light and used immediately after dilution with Sodium chloride 0.9%, 5% glucose, mannitol 10% & ringer's lactate solution
Keep out of reach of children.

Pack
A carton box containing 5 amber (type I)glass ampoules, each containing 2 ml or 4 ml solution in plastic tray and insert leaflet.

Manufacturer& license holder:
Pharaonia Pharmaceuticals (Pharo-Pharma)
New Borg El Arab city – 3rd Industrial zone – block no. 16 – Part (1) – Alexandria – Egypt.

Central Administration for Pharmaceutical care Approval Date: 28/6/2022 Revisor: Dr MarwaMahmoud
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to last approved leaflet " Ondametic 17-5-2020" after warning addition

Dr Marwa 28/6/2022

أوندامبتيك
٤ مجم/ ٢ مللي و ٨مجم/ ٤ مللي
محلول للحقن العضلي أو الوريدي البطيء أو التنقيط الوريدي
(أوندانسيترون)

- يجب قراءة النشرة جيدا قبل البدء في تناول هذا الدواء
- يصح بالاحتفاظ بهذه النشرة لأن المريض قد يحتاج أن يقرأها مرة أخرى
- لو أن المريض لديه اسئلة أخرى فعليه الرجوع للطبيب أو الصيدلي
- إذا تم وصف هذا الدواء لمريض، فلا يجب أن يعطيه لشخص آخر حتى أن كان هذا الشخص يعاني من نفس الأعراض
- إذا ظهرت أي من الأعراض الجانبية فلابد من الرجوع للطبيب أو الصيدلي بما في ذلك أي أعراض جانبية أخرى لم تذكر في هذه النشرة

بيان التركيب:
أوندامبتيك ٤ مجم/ ٢ مللي:
كل أمبول ٢ مللي يحتوي على:
المادة الفعالة
هيدروكلوريد أوندانسيترون ثنائي الماء ٤.٩٨٨ مجم يكافئ ٤ مجم أوندانسيترون.
مواد غير فعالة
كلوريد الصوديوم، حمض الستريك اللامائي، سيترات الصوديوم ثنائي الماء، ماء للحقن

أوندامبتيك ٨ مجم/ ٤ مللي:
كل أمبول ٤ مللي يحتوي على:
المادة الفعالة
هيدروكلوريد أوندانسيترون ثنائي الماء ٩.٧٦ مجم يكافئ ٨ مجم أوندانسيترون
مواد غير فعالة
كلوريد الصوديوم، حمض الستريك اللامائي، سيترات الصوديوم ثنائي الماء، ماء للحقن

ما هو أوندامبتيك ٤ مجم/ ٢ مللي و ٨ مجم/ ٤ مللي و فيما يستخدم؟
يحتوي أوندامبتيك على المادة الفعالة أوندانسيترون و هو ينتمي إلى مجموعة دوائية يطلق عليها مضادات القيء.
يستخدم أوندامبتيك لـ:
- الوقاية من الغثيان و القيء الذي ينتج عن العلاج الكيماوي (في البالغين و الأطفال) أو العلاج الأشعاعي للسرطان (البالغين فقط).
- الوقاية من غثيان و قيء ما بعد العمليات الجراحية.

لابد من سؤال الطبيب، الممرضة أو الصيدلي في حالة وجود شرح إضافي عن هذه الاستخدامات.

ما تريد معرفته قبل استخدام أوندامبتيك
لا تستخدم حقن لأوندامبتيك في حالة:
- **كنت تتناول ابومورفين (يستخدم لعلاج مرض باركنسون) فانه يتعارض الاستخدام المتزامن للأبومورفين مع أوندانسيترون استنادالتقارير عن انخفاض ضغط الدم الشديد وفقدان الوعي عند تناول الأبومورفين مع أوندانسيترون.**

كيف يتم استخدام أونداميتك

يتم اعطاء حقن أونداميتك عادة عن طريق الطبيب أو الممرضة سوف يتم وصف الجرعة اعتماداً على العلاج.

للوقاية من الغثيان و القئ الناتج عن العلاج الكيماوي أو الأشعاعي في البالغين

في يوم العلاج الكيماوي أو الاشعاعي

تبلغ الجرعة المعتادة للبالغين ٨ مجم يتم اعطاءها عن طريق الحقن البطئ في الوريد او العضل قبل العلاج مباشراً، و ٨ مجم اخرى بعد ١٢ ساعة بعد العلاج بالكيماوي، سوف يتم تناول الدواء عن طريق الفم ٨ مجم أوندنسيترون اقراص أو ١٠ مللي اوندنسيترون شراب.

في الأيام التالية:

تبلغ الجرعة المعتادة للبالغين قرص ٨ مجم أو ١٠ مللي شراب مرتين يومياً و قد يستمر ذلك لـ٥ أيام.

إذا كان عادة ما يسبب العلاج الكيماوي أو الأشعاعي غثيان و قئ شديد، سوف يتم إعطاء جرعة اكبر من جرعة اونداميتك المعتادة و هذا ما سوف يقرره الطبيب.

للوقاية من الغثيان و القئ الناتج عن العلاج الكيماوي في الأطفال أكبر من شهر و اليافعين

سوف يقرر الطبيب الجرعة معتمد على حجم الطفل (مساحة الجسم) أو الوزن.

في يوم العلاج الكيماوي

سوف يتم اعطاء الجرعة الأولى في الوريد، قبل علاج الطفل مباشراً بعد العلاج الكيماوي، سوف يتم اعطاء الطفل الدواء عن طريق الفم بعد ١٢ ساعة كشراب أو أقراص من الأوندنسيترون.

في الأيام التالية:

- ٢,٥ مللي (٢ مجم) شراب مرتين يومياً للأطفال الصغار الذين يبلغ وزنهم ١٠ كجم أو أقل.
- قرص واحد ٤ مجم أو ٥ مللي (٤ مجم) شراب مرتين يومياً للأطفال الأضخم و الذين يبلغ وزنهم أكثر من ١٠ كجم.
- قرصين ٤ مجم أو ١٠ مللي (٨ مجم) شراب مرتين يومياً للمراهقين أو ذوي الأحجام الضخمة).
- يمكن اعطاء هذه الجرعات حتى ٥ أيام.

للوقاية و علاج غثيان و قئ ما بعد العمليات

البالغين:

تبلغ الجرعة المعتادة ٤ مجم يتم اعطاءها عن طريق الحقن البطئ في الوريد أو في العضل. سوف يتم اعطاء الجرعة قبل العملية مباشراً.

الأطفال:

سوف يقرر الطبيب الجرعة للأطفال أكبر من شهر و اليافعين. سوف تبلغ الجرعة القصوى ٤ مجم للحقن البطئ في الوريد. سوف يتم اعطاء الجرعة قبل العملية مباشراً.

المرضى المصابين بمشاكل متوسطة أو شديدة بالكبد

لا يجب أن تتجاوز الجرعة اليومية الكلية ٨ مجم.

في حالة استمرار الشعور بالتعب أو التعب

يبدأ أونداميتك العمل بعد الحقن بقليل. لابد من الرجوع إلى الطبيب أو الممرضة في حالة استمرار التعب أو الشعور بالتعب.

في حالة أستخدام أونداميتك أكثر من اللازم

بما أن يتم إعطاء جرعة أونداميتك عن طريق الطبيب أو الممرضة فأنه من غير المألوف حدوث فرط للجرعة. يتم الرجوع للطبيب أو الممرضة في حالة الأعتقاد بأخذ كمية كبيرة أو نسيان جرعة.

الاثار الجانبية المحتملة

- وجود حساسية (فرط الحساسية) للأوندنسيترون او أي من المكونات الأخرى للأونداميتيك.

في حالة الشك، يتم الرجوع إلى الطبيب، الممرضة أو الصيدلي قبل الحقن بالأونداميتيك.

التحذيرات و الاحتياطات

يتم الرجوع للطبيب، الممرضة او الصيدلي قبل استخدام حقن أونداميتيك إذا:

- عانيت في أي وقت من مشاكل في القلب (مثل قصور القلب الاحتقاني الذي يسبب ضيقًا في التنفس وتورم الكاحلين)
- كان لديك عدم انتظام ضربات القلب (عدم إنتظام ضربات القلب).
- كان لديك حساسية من الأدوية المشابهة لأوندانسيترون ، مثل جرانيسيترون أو بالونوسترون وجود مشاكل بالكبد.
- كان لديك انسداد بالقناة الهضمية.
- كان لديك مشاكل في مستويات الأملاح في الدم ، مثل البوتاسيوم والصوديوم والمغنيسيوم.
- إذا لم تكن متأكدًا من ان أي مما سبق ينطبق عليك ، فتحدث إلى الطبيب أو الممرضة أو الصيدلي قبل تناول حقن أونداميتيك .

أخبر طبيبك أو الصيدلي فورًا إذا ظهرت عليك أي من هذه الأعراض أثناء وبعد العلاج بإستخدام أونداميتيك

إذا كنت تعاني من ألم مفاجئ في الصدر أو ضيق في الصدر (إقفار عضلة القلب).

الأدوية الأخرى و أونداميتيك

يتم إخبار الطبيب، الممرضة أو الصيدلي في حالة تناولك أو تناولت مؤخرًا أو قد يتم تناول أي من هذه الأدوية. يشمل ذلك الأدوية التي يتم صرفها بدون روشتة و أدوية الأعشاب. هذا لأن أونداميتيك قد يؤثر على طريقة عمل بعض الأدوية. و أيضاً قد تؤثر بعض الأدوية الأخرى على طريقة عمل أونداميتيك .

يتم إخبار الطبيب، الممرضة أو الصيدلي على وجه الخصوص في حالة تناول أي من الأدوية الاتية:

- الكاربامازيبين أو الفنيتوين المستخدمة لعلاج الصرع
- ريفامبيسين الذي يستخدم لعلاج العدوى مثل مرض السل
- مضادات الحيوية مثل إريثرومايسين أو كيتاكونازول
- الأدوية المستخدمة لعلاج عدم انتظام ضربات القلب
- أدوية حاصرات بيتا المستخدمة لعلاج بعض مشاكل القلب مثل الألم والقلق أو منع الصداع النصفي
- ترمادول، مسكن قوي للألم.
- الأدوية التي تؤثر على القلب (مثل هالوبيريدول أو ميثادون).
- أدوية المستخدمة في علاج السرطان (أنثراسيكلين و تراستوزوماب).
- مثبطات امتصاص السيروتونين الانتقائية(SSRIs) التي تستخدم لعلاج الإكتئاب و/أو القلق تشمل فلوكستين، باروكسيتين، سيرترالين، فلوفوكسامين، سيتالوبرام و ايكسيتالوبرام.
- مثبطات استرداد السيروتونين والنورابينفرين(SNRIs) التي تستخدم لعلاج الإكتئاب و/أو القلق تشمل فينلافاكسين، ديلوكسيتين.

لا بد من الرجوع إلى الطبيب، الممرضة أو الصيدلي في حالة الشك من وجود الحالات السابقة قبل الحقن بأونداميتيك .

لا يجب اعطاء حقن أونداميتيك في نفس السرنجة أو بالتنقيط كمثل اي دواء أخرى.

الحمل و الرضاعة

لا يجب ان تستخدم أونداميتيك خلال الأشهر الثلاث الأولى من الحمل. هذا لانه يمكن ان يزيد قليلا من خطر ولادة طفل بشفة مشقوقة و/ أو حنك مشقوق.

اذا كنت حاملا بالفعل، تفكري في انك قد تكونين حاملا او تخططين لانجاب طفل، اطلبي من طبيبك او الصيدلي النصيحة قبل تناول أونداميتيك .

اذا كنتي لديك إمكانية الانجاب، فقد ينصح باستخدام وسائل منع الحمل الفعالة.

لا تقومي القيام بالرضاعة الطبيعية اذا كنت تتلقين أوندانسيترون. وذلك لان كميات صغيرة تنتقل إلى حليب الام. إسال طبيبك للحصول على المشورة.

مثل جميع الأدوية ، يمكن أن تتسبب حقن إيميرست في حدوث اثار جانبية ، على الرغم من عدم حدوثها لدى الجميع.

تفاعلات الحساسية:
لابد من الرجوع إلى الطبيب أو إحدى افراد الطاقم الطبي مباشراً في حالة وجود تفاعلات الحساسية. قد تشمل هذه العلامات:

- الأزيز المفاجئ و الم الصدر أو ضيق الصدر.
- انتفاخ جفون العين، الوجه، الشفتين، الفم أو اللسان.
- بقع حمراء مثيرة للهيجان الجلدي أو كتل تحت الجلد في أي مكان بالجسم.
- تدهور الصحة

اثار جانبية أخرى تشمل:
شائعة جداً (قد تؤثر على أكثر من ١/١٠ أشخاص)

- صداع

شائع (قد يؤثر حتى ١/١٠ أشخاص)

- الشعور بالدفئ و تدفق الدم في الوجه.
- إمساك.
- تغيير في نتائج اختبار وظائف الكبد (في حالة أخذ حقن أونداميتيك مع دواء يسمى سيمبلاتين في غير ذلك يصبح هذا الاثر الجانبي غير شائع).
- تهيج و احمرار في مكان الحقن.

شائع (قد تؤثر حتى ١/١٠٠ شخص)

- الفواق.
- انخفاض ضغط الدم التي قد تجعلك تشعر بالإغماء أو الدوخة.
- عدم انتظام ضربات القلب.
- ألم بالصدر.
- النوبات.
- حركات جسد غير طبيعية أو اهتزاز.

نادرة (قد تؤثر حتى ١/١٠٠٠ شخص)

- الشعور بالدوخة أو دوار الرأس.
- عدم وضوح الرؤية.
- اضطرابات بإيقاع القلب (قد يسبب أحياناً فقدان مفاجئ للوعي)

نادرة جداً (قد تؤثر حتى ١/١٠٠٠٠ شخص)

- ضعف الرؤية أو فقدان مؤقت للبصر ، والذي عادة ما يعود في غضون ٢٠ دقيقة

نقص تدفق الدم لعضلة القلب:
•ألم مفاجئ في الصدر أو
ضيق الصدر

الإبلاغ عن الآثار الجانبية
اذا اصبت بأي أثار جانبية، تحدث الى طبيبك أو الصيدلي. هذا يتضمن أي أثار جانبية محتملة غير مذكورة في هذه النشرة.
يمكنك أيضا الإبلاغ عن الآثار الجانبية مباشرة عن طريق (انظر التفاصيل أدناه). الإبلاغ عن الآثار الجانبية يساعد في توفير المزيد من المعلومات حول سلامة هذا الدواء.
مركز اليقظة الصيدلية المصري- هيئة الدواء المصرية:
بريد الكتروني: pv.followup@edaegypt.gov.eg

من خلال الإبلاغ عن الآثار الجانبية ، يمكنك المساعدة في توفير مزيد من المعلومات حول سلامة هذا الدواء.

التخزين:
يتم التخزين عند درجة حرارة لا تزيد عن ٣٠ درجة حرارة مئوية و يستخدم مباشرةً بعد التخفيف بكلوريد الصوديوم ٠,٩٪، جلوكوز ٥%، مانيتول ١٠٪ و محلول الرينجر لاكتات على أن يتم التخزين فى درجة حرارة لا تزيد عن ٣٠ درجة حرارة مئوية بعيدا عن الضوء.
يحفظ بعيد عن متناول الأطفال.
مدة الصلاحية : عامان

العبوة:
علبة كرتون تحتوي على ٥ امبولات زجاج كهرماني اللون (من النوع الأول) كل منها يحتوى على ٢ مللي او ٤ مللي محلول في درج بلاستيك و نشرة داخلية.

الشركة المصنعة ومالك المستحضر:
الشركة الفرعونية للأدوية (فارو فارما)
مدينة برج العرب الجديدة- المنطقة الصناعية الثالثة- قطعة رقم(١)- الإسكندرية-ج.م.ع.