ONDANSETRON 4mg MIAMED
ONDANSETRON 8mg MIAMED

Solution for intramuscular injection and intravenous injection and infusion

Composition:
Each 2mL of **ONDANSETRON 4mg MIAMED** solution contains 4mg Ondansetron as (4.988mg Ondansetron Hydrochloride Dihydrate)
Each 4mL of **ONDANSETRON 8mg MIAMED** solution contains 8mg Ondansetron as (9.976mg Ondansetron Hydrochloride Dihydrate)

Excipients:
Sodium Chloride, Citric Acid Monohydrate, Sodium Citrate & Water for injection USP QS to 2ml or 4ml.

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 & vomiting. The role of ondansetron in opiate-induced emesis is not yet established.

Indications:
ONDANSETRON MIAMED solution is indicated in the following cases:
Adults:
- Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
- Prevention and treatment of post-operative nausea and vomiting (PONV).

Pediatric Population:
- Management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months.
- Prevention and treatment of post-operative nausea and vomiting in children aged ≥1 month.

Contraindications:
ONDANSETRON MIAMED solution is contraindicated in the following cases:
- Concomitant use with apomorphine.
- Hypersensitivity to any component of the preparation.

Warnings and precautions:
- 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, bradyarrhythmia or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.
- Hypokalemia 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.
- Pediatric Population: Pediatric 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 5mg/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.

Side effects:
Immune system disorders:
Rare: Immediate hypersensitivity reactions, including anaphylaxis.
Nervous system disorders:
Very common: Headache.
Uncommon: Seizures, movement disorders (including extrapyramidal reactions)
Rare: Dizziness predominantly during rapid IV administration.
Eye disorders:
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
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 and thoracic disorders:
Uncommon: Hiccups.
Gastrointestinal disorders:
Common: Constipation.
Hepatobiliary disorders:
Uncommon: Asymptomatic increases in liver function tests.
General disorders and administration site conditions:
Common: Local IV injection site reactions.

Drug 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 metabolized by multiple hepatic cytochrome P450 enzymes: CYP_3A_4, CYP_2D_6 and CYP_1A_2. Due to the multiplicity of metabolic enzymes capable of metabolizing ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g., CYP_2D_6 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 co-administered 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.
- 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).
- Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.
- In patients treated with potent inducers of CYP_3A_4 (i.e. phenytoin, carbamaze pine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.
- Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

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 fetus, the course of gestation and peri- & post-natal development.
- 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. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

Dosage and administration:
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 MIAMED** should be flexible in the range of 8-32 mg a day.
Emetogenic chemotherapy and radiotherapy:
Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.
For most patients receiving emetogenic chemotherapy or radiotherapy, 8mg **ONDANSETRON MIAMED** should be administered as a slow intravenous injection (in not less than 30 seconds) or intramuscular injection, immediately before treatment, followed by 8mg orally twelve hourly.
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.
  - A single dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injection (in not less than 30 seconds) or intramuscular doses of 8mg four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
  - A maximum initial intravenous dose of 16mg diluted in 50-100ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of **ONDANSETRON MIAMED** may be followed by two additional 8mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.
– A single dose greater than 16mg 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 **ONDANSETRON MIAMED** in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexametha sone sodium phosphate, 20mg 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.

Pediatric:
CINV in children aged ≥ 6 months and adolescents:
- The dose for CINV can be calculated based on body surface area (BSA) or weight.
- In pediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50ml of saline or other 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.
- **ONDANSETRON MIAMED** injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and infused intravenously over not less than 15 minutes.

Dosing by BSA:
- **ONDANSETRON MIAMED** should be administered immediately before chemotherapy as a single intravenous dose of 5mg/m². The single intravenous dose must not exceed 8mg.
- 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 32mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥6 months and adolescents:

BSA	Day 1	Days 2-6
< 0.6 m²	5 mg/m² IV plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0.6 m² to ≤ 1.2 m²	5 mg/m² IV plus 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs
> 1.2 m²	5 mg/m² or 8 mg IV plus 8 mg syrup or tablet after 12 hours	8 mg syrup or tablet every 12 hours

Dosing by bodyweight:
- Weight-based dosing results in higher total daily doses compared to BSA-based dosing.
- **ONDANSETRON MIAMED** should be administered immediately before chemotherapy as a single intravenous dose of 0.15mg/kg. The single intravenous dose must not exceed 8mg. 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 32mg.

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

Weight	Day 1	Days 2-6
≤ 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

Elderly:
- In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100ml of saline or other compatible infusion fluid and infused over 15 minutes.
- In patients 75 years of age or older, the initial intravenous dose of **ONDANSETRON MIAMED** should not exceed 8 mg. All intravenous doses should be diluted in 50-100ml of saline or other compatible infusion fluid and infused over 15 minutes. The initial dose of 8mg may be followed by two further intravenous doses of 8mg, 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 8mg should not be exceeded.

Post-operative nausea and vomiting:
Adults:
- For the prevention of PONV:
  - Ondansetron can be administered orally or by intravenous or intramuscular injection.
  - **ONDANSETRON MIAMED** may be administered as a single dose of 4mg given by intramuscular or slow intravenous injection at induction of anesthesia.
- For treatment of established PONV:
  - A single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Pediatric population:
- PONV in children aged ≥ 1 month and adolescents:
  - For prevention of PONV in pediatric patients having surgery performed under general anesthesia, a single dose of **ONDANSETRON MIAMED** may beadministered by slow intravenous injection (not less than 30 seconds) at a doseof 0.1 mg/kg up to a maximum of 4mg either prior to, at or after induction of anesthesia.
  - There are no data on the use of **ONDANSETRON MIAMED** in the treatment of PONV in children below 2 years of age.

Elderly:
- There is limited experience in the use of **ONDANSETRON MIAMED** in the prevention and treatment of PONV in the elderly, however **ONDANSETRON MIAMED** 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 MIAMED** 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 8mg should not be exceeded and therefore parenteral or oral administration is recommended.

Overdose:
Symptoms & Signs: 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.

Treatment: There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic & supportive therapy should be given as appropriate.
- 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.

Storage conditions:
- Store at temperature not exceeding 30°C, Protected from light.
- If the product diluted, store at refrigerator (2-8)°C for no more than 24 hours.
- Keep out of reach of children.

Packaging:
ONDANSETRON MIAMED solution is filled in polyethylene plastic ampoule 2ml for 4mg Ondansetron & 4ml for 8mg Ondansetron, each 5 ampoules overwrapped with Aluminum foil packed in carton box with a leaflet, each caton box contains 5 or 100 ampoule.

Produced by MIAMED Pharmaceutical Industries –Damascus countryside –Syria

This is a medicament
- A medicament is a product but unlike any other products.
- A medicament is a product which affect your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
Keep medicaments out of reach of children

Council of Arab Health Ministers — Arab pharmacist Association

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