

ONDANSETRON

FRENVO

4 mg/5 mL Syrup

Antiemetic/Antinauseant

[Serotonin (5HT₃) Antagonist]

FORMULATION:

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Each 5ml syrup contains:
Ondansetron 4 mg
(as Ondansetron hydrochloride dihydrate)

PRODUCT DESCRIPTION:

Clear, colourless syrup with strawberry flavour.

PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT₃) antagonist

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, randomized, 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.

Pediatric 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 hrs. 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= 28). 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 ≥ 3 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 (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p < 0.0001).

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.

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing 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 IM and IV 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 show a 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 pediatric 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 months was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 months 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 pediatric 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 pediatric 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 intravenous 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 IV 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 (15-32 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.

INDICATIONS:

Ondansetron Syrup is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Ondansetron Syrup is also indicated for the prevention of post-operative nausea and vomiting (PONV).

For treatment of established PONV, administration by injection is recommended.

POSODOLOGY AND METHOD OF ADMINISTRATION:

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

CINV and RINV in Adults:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Emetogenic chemotherapy and radiotherapy: Ondansetron can be given by oral administration.

The recommended oral dose is 10 mL (8 mg) 1-2 hours before treatment, followed by 10 mL (8 mg) orally 12 hours later.

For highly emetogenic chemotherapy: a single dose of up to 30 mL (24 mg) Ondansetron taken with 12 mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used.

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

The recommended dose for oral administration is 10 mL (8 mg) to be taken twice daily.

Pediatric 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 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.

There are no data from controlled clinical trials on the use of Ondansetron in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of Ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by BSA:

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/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 32 mg.

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

BSA	Day 1 (a, b)	Days 2-6 (b)
< 0.6m ²	5mg/m ² IV plus 2mg syrup after 12 hours	2mg (2.5 mL) syrup every 12 hours
0.6m ² to 1.2m ²	5mg/m ² IV plus 4mg syrup or tablet after 12 hours	4mg syrup (5 mL) or tablet every 12 hours

a The intravenous dose must not exceed 8 mg.

b The total dose over 24 hours must not exceed adult dose of 32 mg

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8mg.

Two further intravenous doses may be given in 4-hourly intervals.

Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2). The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

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

Weight	Day 1 (a, b)	Days 2-6 (b)
10kg	Up to 3 doses of 0.15mg/kg every 4 hours	2mg (2.5 mL) syrup every 12 hours
> 10kg	Up to 3 doses of 0.15mg/kg every 4 hours	4mg (5 mL) syrup every 12 hours

a The intravenous dose must not exceed 8mg.

b The total dose over 24 hours must not exceed adult dose of 32 mg.

Elderly:

Ondansetron is well tolerated by patients over 65 years. No alteration of oral dose or frequency of administration is required.

Post operative nausea and vomiting (PONV).

Adults:

For the prevention of PONV: Ondansetron can be administered orally

For oral administration: 20 mL (16 mg) one hour prior to anaesthesia.

For the treatment of established PONV: Intravenous or intramuscular administration is recommended.

Pediatric population:

PONV in children aged ≥ 1 month and adolescents

Oral formulation:

No studies have been conducted on the use of orally administered Ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow IV injection (not less than 30 seconds) is recommended for this purpose.

There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

Elderly:

There is limited experience in the use of Ondansetron in the prevention and treatment of PONV in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

For both indications:

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 10 mL (8 mg) should not be exceeded.

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.

Method of administration:

- Use the 2.5-5 mL double-ended spoon supplied in the pack (see below) to measure the required dose.

- Swallow the solution.

- Wash the spoon with clean water after taking every dose.

- Once measured, the solution should be consumed within 3 hours

Double-ended Spoon



CONTRAINDICATION:

Hypersensitivity to any of the ingredients in the product.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

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.

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 subacute 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 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.

Excipient warnings:

This medicinal product contains:

Sorbitol (E420): This medicinal product contains 2100 mg sorbitol in each 5 mL dose which is equivalent to 420 mg/mL. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Sodium benzoate (E211): This medicinal product contains 6mg sodium benzoate in each 5 mL dose which is equivalent to 1.2 mg/mL.

Propylene glycol (E1520): This medicinal product contains 14.1 mg/5 mL propylene glycol in each 5ml dose which is equivalent to 2.82 mg/mL.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per 5 mL dose, that is to say essentially 'sodium-free'.

FERTILITY, PREGNANCY AND LACTATION:

Women of childbearing potential should consider the use of contraception.

Pregnancy

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

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48).

The available epidemiological studies on cardiac malformations show conflicting results. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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

Breast-feeding

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.

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.

ADVERSE DRUG REACTIONS:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <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 during rapid IV administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare:	Transient blindness predominantly during IV administration ²⁾
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. ³⁾

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.

Paediatric population

The adverse event profile in children and adolescents was comparable to that seen in adults.

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 national reporting system.

OVERDOSE AND TREATMENT:**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.

Treatment

There is no specific antidote for Ondansetron, therefore in all cases of suspected overdose, symptomatic and 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.

Paediatric population

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

Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CAUTION:

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

KEEP ALL MEDICINES OUT OF CHILDREN'S REACH.**STORAGE CONDITION:**

Store at temperatures not exceeding 30°C.

AVAILABILITY:

60 mL capacity (50 mL net content) Ph. Eur. Type III amber glass bottle with white polypropylene/polyethylene cap and with dosing device of 2.5 mL-5 mL double ended spoon (Box of 1's)

DR-XY48494

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