NOVARTIS

Zofran®

Composition

Active substances

Film-coated tablets/syrup/concentrate for solution for infusion/solution for injection: Ondansetron (as ondansetron hydrochloride dihydrate).

Melt oral lyophilisate: Ondansetron.

Excipients

Film-coated tablets: Lactose (anhydrous), microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, methyl hydroxypropyl cellulose, Opaspray yellow M1-8429, purified water.
Melt oral lyophilisate: Gelatin, mannitol, aspartame, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, strawberry flavour, purified water.

Syrup: Citric acid anhydrase, sodium citrate dihydrate, sodium benzoate, sorbitol solution, strawberry flavour, purified water.

Solution for injection: Sodium chloride, citric acid monohydrate, sodium citrate, water for injections.
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

4 mg and 8 mg film-coated tablets.
4 mg and 8 mg Melt oral lyophilisate.
4 mg/5 ml syrup.
2 mg/ml parenteral solution.

Indications/Potential uses

Treatment of chemotherapy-induced nausea and vomiting (CINV) in adults and in children aged ≥6 months.
Treatment of radiotherapy-induced nausea and vomiting (RINV) in adults.
Prevention and treatment of post-operative nausea and vomiting (PONV) in adults and in children aged ≥1 month.
If post-operative nausea and/or vomiting are unlikely, routine prophylaxis is not recommended, as with other anti-emetics.
If post-operative nausea and/or vomiting needs to be prevented, Zofran administration is recommended even if the incidence of post-operative nausea and/or vomiting is low.

Dosage/Administration

Adults

Moderately emetogenic chemotherapy (cyclophosphamide, doxorubicin, carboplatin) and radiotherapy-induced nausea and vomiting:
Administer 8 mg as a parenteral infusion immediately before chemotherapy or radiotherapy (over a minimum of 15 minutes). 8 mg can also be administered orally 1 to 2 hours before starting treatment.
Treatment should then be continued with an oral dose of max. 8 mg every 12 hours for a maximum of 5 days.

Highly emetogenic chemotherapy (cisplatin):
Administer 8 mg as an infusion immediately before chemotherapy over a minimum of 15 minutes. (For information on miscibility/compatibility with other solutions for infusion, see "Other information").
Alternative dosing regimens for patients with high emetogenic risk:

- Immediately before starting chemotherapy, administer 8 mg as an infusion over a minimum of 15 minutes followed by 2 further parenteral doses of 8 mg each (infused over a minimum of 15 minutes) 4 hours apart or as a continuous infusion of 1 mg/h for up to 24 hours.
- Immediately before starting chemotherapy, administer 16 mg as an infusion (diluted with 50-100 ml) over a minimum of 15 minutes followed by 2 further parenteral doses of 8 mg each (infused over a minimum of 15 minutes) 4 hours apart or as a continuous infusion of 1 mg/h for up to 24 hours. A single dose higher than 16 mg should not be administered (see "Warnings and precautions").

IV doses above 8 mg up to a maximum of 16 mg should be diluted before use in 50-100 ml of solution for infusion and infused over a minimum of 15 minutes (see "Other information").
All three treatments should then be continued with an oral dose of max. 8 mg every 12 hours for 3 (maximum of 5) days.
The effect of Zofran may be intensified by dexamethasone sodium phosphate (20 mg IV 30-45 minutes before chemotherapy).

Post-operative nausea and vomiting in adults:
Prevention: A single parenteral dose of 4 mg by slow IV injection during induction of anaesthesia.
Treatment: A single parenteral dose of 4 mg by slow IV injection.
The injection time must not be less than 30 seconds. It should preferably last for 2 to 5 minutes.
Use of oral ondansetron to prevent or treat post-operative nausea and vomiting has not been studied. Administration as an IV injection is recommended for this purpose.

Children and adolescents
CINV in children and adolescents aged from 6 months to 17 years:
Studies conducted in children and adolescents demonstrate good efficacy and tolerability on the following regimen:
Children aged from 6 months to 17 years are administered three IV doses of 0.15 mg ondansetron/kg body weight. The first dose is administered 30 minutes before moderately to highly emetogenic chemotherapy, followed by two further parenteral doses (0.15 mg/kg) 4 and 8 hours, respectively, after the first dose (infusion over a minimum of 15 minutes).
Oral follow-up treatment day 2 + 3 (-5):
Children 0.6 – 1.2 m²: 4 mg orally every 8 hours.
Children >1.2 m²: 8 mg orally every 8 hours.

Post-operative nausea and vomiting in children and adolescents aged from 1 month to 17 years:
Prevention: During or after induction of anaesthesia, 0.1 mg/kg body weight (max. 4 mg) by slow IV injection.
Treatment: 0.1 mg/kg body weight (max. 4 mg) by slow IV injection.
Since clearance is reduced in infants (<4 months) compared to older children and since repeat dosing (e.g. to treat PONV) has not been studied in this age group, Zofran must not be administered repeatedly in this age group (see "Pharmacokinetics").
The injection time must not be less than 30 seconds. It should preferably last for 2 to 5 minutes.
Use of oral ondansetron to prevent or treat post-operative nausea and vomiting has not been studied. Administration as an IV injection is recommended for this purpose.

Use of Melt oral lyophilisate Melt oral lyophilisate are a freeze-dried, fast dispersing oral dosage form. Place the Melt oral lyophilisate on top of the tongue, where it will disperse within seconds, then swallow.
Do not push the Melt oral lyophilisate through the blister foil. Peel back the blister foil and carefully remove the Melt oral lyophilisate from the blister.

Special populations
Elderly patients
CINV and RINV
Oral formulation
Adjusting the oral dose or the dosing frequency is not required.

IV formulation
In patients 65 years of age or older, all IV doses should be diluted with 50 to 100 ml physiological saline solution or with other compatible solutions (see "Other information") and infused over 15 minutes and, if repeated, given no less than 4 hours apart.
In patients 65 to 74 years of age, the initial IV dose of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart.
In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes, and given no less than 4 hours apart (see "Pharmacokinetics – Pharmacokinetics in special populations – Elderly patients").

After the initial parenteral doses, treatment may be continued with an oral dose of max. 8 mg every 12 hours *for 3 to a maximum of* 5 days.
Severe toxic effects have not been reported yet; however, clinical experience is limited. Due to age-related reduction in hepatic function, the metabolism and clearance of ondansetron may decrease, leading to increased ondansetron exposure, particularly after repeated dosing. For this reason, a single IV dose of 8 mg should not be exceeded in elderly patients (≥75 years).

Post-operative nausea and vomiting in elderly patients
There is little experience with Zofran in the treatment of post-operative nausea and vomiting in elderly patients.

Hepatic impairment
The plasma clearance of an 8 mg IV dose of Zofran was significantly reduced and the serum half-life was increased in patients with severe hepatic impairment. A daily dose of 8 mg should not be exceeded in patients with moderate to severe hepatic impairment.

Patients who are poor metabolisers of sparteine/debrisoquine
The elimination half-life of ondansetron is not altered in patients who are poor metabolisers of sparteine and debrisoquine. Therefore, a reduction of the normal dose is not required in these patients.

Contraindications

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.
Patients with known hypersensitivity to any component of Zofran should not take the product.

Warnings and precautions

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT$_3$ receptor antagonists.
Hypersensitivity reactions may only occur after repeat administration of Zofran (see "Adverse effects").
As ondansetron increases large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following Zofran administration (isolated cases of ileus are known, especially related to underlying intestinal disease or treatment with certain cytostatic agents, e.g. vinca alkaloids).
Melt oral lyophilisate contain aspartame and should therefore be taken with caution in patients with phenylketonuria.
Doses up to 4 mg may be administered to adults by slow IV injection. The injection time must not be less than 30 seconds. It should preferably last for 2 to 5 minutes.
Ondansetron prolongs the QT interval in a dose-dependent manner (see "Properties/Action"). 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 QTc prolongation. ECG monitoring is recommended. This includes patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.
Myocardial ischaemia and even myocardial infarction have been reported in ondansetron-treated patients with or without pre-existing cardiovascular risk factors/disease, including younger patients. In some cases, predominantly with intravenous use, symptoms occurred immediately after use, partially resolving following prompt treatment. Coronary artery spasm appears to be the most common cause. Therefore, caution is required during and after use of ondansetron and in the event of cardiac symptoms the patient must immediately undergo further cardiological assessment and be treated as necessary (see "Adverse effects").
Hypokalaemia or hypomagnesaemia should be treated prior to ondansetron administration.
Serotonin syndrome has been described following the co-administration of ondansetron and other serotonergic drugs (see "Interactions"). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate monitoring of the patient is advised.
Since clearance is reduced in infants (<4 months) compared to older children and since repeat dosing (e.g. to treat PONV) has not been studied in this age group, Zofran must not be administered repeatedly in this age group (see "Pharmacokinetics").
Zofran film-coated tablet:
Zofran film-coated tablets contain less than 1 mmol (23 mg) of sodium per tablet, making them practically "sodium-free".
Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.
Melt oral lyophilisate:
Melt oral lyophilisate contains 0.625 mg aspartame/4 mg tablet and 1.25 mg aspartame/8 mg tablet. Aspartame is a source of phenylalanine. In patients with phenylketonuria, phenylalanine may accumulate, which the body cannot sufficiently metabolise. Melt oral lyophilisate contains 0.00002 mg benzyl alcohol/4 mg tablet and 0.00004 mg benzyl alcohol/8 mg tablet. Benzyl alcohol may cause allergic reactions, including delayed reactions. Benzyl alcohol has been associated with a risk of severe adverse effects in infants, including breathing problems ("gasping syndrome"). There is an increased risk in infants due to accumulation.
Due to the risk of accumulation and toxicity ("metabolic acidosis") large amounts of benzyl alcohol should be used with caution and only when absolutely necessary, particularly in those with hepatic or renal impairment.
Melt oral lyophilisate contains less than 1 mmol (23 mg) of sodium per tablet, making it practically "sodium-free".
Zofran syrup:
Zofran syrup contains less than 1 mmol (23 mg) of sodium per 5 ml syrup, making it practically "sodium-free". Zofran syrup contains 0.0126 mg benzyl alcohol/5 ml syrup. Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been associated with a risk of severe adverse effects in infants, including breathing problems ("gasping syndrome"). May cause allergic reactions, including delayed reactions.
Due to the risk of accumulation and toxicity ("metabolic acidosis") large amounts of benzyl alcohol should be used with caution and only when absolutely necessary, particularly in those with hepatic or renal impairment.
Zofran syrup contains 2.1 g sorbitol per measuring spoon (5 ml). Sorbitol is a source of fructose. The additive effect of co-administered medicinal products containing sorbitol (or fructose) and the dietary intake of sorbitol (or fructose) must be taken into consideration.
Concentrate for solution for infusion/solution for injection: Contains less than 1 mmol (23 mg) of sodium per glass ampoule, making it practically "sodium-free".

Interactions

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicinal products commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol or propofol.
Ondansetron is metabolised by multiple hepatic cytochrome P450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Since ondansetron's metabolism can be carried out by a number of metabolic enzymes, inhibition or reduced activity of one of these enzymes (e.g. CYP2D6 genetic deficiency) is, under normal circumstances, expected to be compensated by other enzymes and expected to result in little or no significant change in overall ondansetron clearance or dose requirement.
Caution should be exercised when ondansetron is co-administered with medicinal products that prolong the QT interval and/or cause electrolyte abnormalities (see "Warnings and precautions").

Apomorphine:
Based on reports of profound hypotension and loss of consciousness when ondansetron is administered with apomorphine hydrochloride, co-administration 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 increased and ondansetron blood concentrations decreased.

Serotonergic drugs (e.g. SSRIs and SNRIs)
Serotonin syndrome including cognitive disorders and behavioural changes, autonomic instability and neuromuscular abnormalities) has been described following the co-administration of ondansetron and other serotonergic drugs, including selective serotonin re-uptake inhibitors (SSRIs) and serotonin and noradrenaline re-uptake inhibitors (SNRIs) (see "Warnings and precautions").

Tramadol:
Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol due to a pharmacodynamic interaction on the 5-HT$_3$ receptor.

Pregnancy/Breast-feeding

Pregnancy
In human epidemiological studies an increase in cleft lip/palate was observed in newborn children born of women who had been administered ondansetron during the first trimester of pregnancy. The epidemiological studies showed contradictory results regarding cardiac malformations (see "Human data" below).
Reproduction studies with rats and rabbits did not show evidence of a direct or indirect harmful effect in terms of reproductive toxicity (see "Preclinical data").
The use of ondansetron during pregnancy is not recommended.

Human data
In three epidemiological studies in the USA the risk of specific congenital malformations, including cleft lip/palate and cardiac malformations in children whose mother had been treated with ondansetron in the first trimester of pregnancy, was assessed.
A cohort study with 88,467 pregnant woman treated with ondansetron showed an increased risk of cleft lip/palate (3 additional cases per 10,000 women treated, adjusted relative risk (RR) 1.24 (95% CI: 1.03-1.48)) with no clear increase in the risk of cardiac malformations. In a separately published subgroup analysis with 23,877 pregnant women the use of intravenous ondansetron was not associated with an increased risk of cleft lip/palate or cardiac malformations.
In a case-control study using population-based registries of birth defects with 23,200 cases from two data sets, an increased risk of cleft palate was determined in one data set, while no increased risk was found in the other data set. No increased risk of cardiac malformations was determined in this study.
In the second cohort study with 3,733 pregnant women the use of ondansetron was associated with an increased risk of ventricular septal defect (adjusted RR 1.7 (95% CI 1.0-2.9)). However, no statistically significant increase in the risk of cardiac malformations was established.

Breast-feeding
It is not known whether Zofran is transferred into human milk. There are no data on the effects of Zofran on the breast-fed child or the effects of Zofran on milk production. However, ondansetron has been detected in the milk in animal studies. Nursing mothers should therefore not be treated with Zofran or should not breast-feed their babies.

Contraception
A pregnancy test should be performed on women of childbearing potential prior to the start of treatment with Zofran.
Women of childbearing potential should be advised that Zofran may harm the developing fetus. Sexually active women of childbearing potential are recommended to use a reliable method of contraception (methods that result in less than 1% pregnancy rates) during treatment with Zofran and for two days after stopping treatment.

Fertility
Zofran has no effect on fertility.

Effects on the ability to drive and to use machines

In psychomotor tests, ondansetron did not impair motor performance nor cause sedation.

Adverse effects

Adverse effects are listed below according to organ system and frequency. Frequencies are defined as follows: *Very common* (≥1/10), *common* (≥1/100 to <1/10), *uncommon* (≥1/1,000 to <1/100), *rare* (≥1/10,000 to <1/1,000), *very rare* (<1/10,000).
The data on very common, common and uncommon adverse effects are derived from clinical trials, taking background incidences in the placebo groups into account. Rare and very rare adverse effects were generally determined from spontaneous post-marketing reports.

Immune system disorders
Rare: Allergic type-1 hypersensitivity reactions, including urticaria, angioedema, bronchospasm, dyspnoea, anaphylaxis.

Nervous system disorders
Very common: Headache.
Uncommon: Movement disorders (including extrapyramidal reactions such as oculogyric crisis/dystonia and dyskinesia without evidence of permanent clinical sequelae, seizures).
Rare: Dizziness predominantly during rapid IV administration.

Eye disorders
Rare: Transient visual disturbances (e.g. blurred vision), predominantly during IV administration.
Very rare: Transient amaurosis, predominantly during IV administration.
The majority of the cases of amaurosis reported resolved within 20 minutes. Most patients had previously received chemotherapeutic agents, including cisplatin. Some cases were reported as cortical in origin.

Cardiac disorders
Uncommon: Arrhythmias, angina pectoris with or without ST segment depression, bradycardia.
Rare: QT prolongation (including torsade de pointes).

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Uncommon: Constipation as a result of the increased large bowel transit time.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests (mainly in patients on chemotherapy with cisplatin).

Skin and subcutaneous tissue disorders
Very rare: Toxic epidermal necrolysis (TEN).

General disorders and administration site reactions
Common: IV injection site hypersensitivity reactions (such as redness, pruritus, urticaria), in rarer cases spreading along the veins or as a generalised reaction. Phlebitis and thrombophlebitis were also observed.

Post-marketing adverse effects
The following adverse drug reactions have been derived from post-marketing experience with Zofran via spontaneous reports and literature cases. As these adverse effects are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency, which is therefore categorised as "not known" (cannot be estimated from the available data).

Cardiac disorders:
Frequency not known: Myocardial ischaemia, acute myocardial infarction.
Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product.

Overdose

Symptoms
There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those in patients receiving normal doses (see "Adverse effects"). Ondansetron prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.
Symptoms consistent with serotonin syndrome have been reported in children following oral overdose.

Treatment
There is no specific antidote for ondansetron. In the event of suspected overdose, suitable symptomatic and supportive therapy is indicated.
The use of ipecacuanha to treat an ondansetron overdose is not recommended as it must be assumed that the patients will not be sufficiently responsive to ipecacuanha due to the anti-emetic effect of ondansetron.

Properties/Action

ATC code:
A04AA01

Mechanism of action
Ondansetron is a highly effective, selective 5-HT$_3$ receptor antagonist. Its precise mechanism of action in controlling nausea and vomiting is not known.
Chemotherapy and radiotherapy may cause serotonin (5-HT) to be released into the gastrointestinal tract, particularly the small intestine, initiating reflex vomiting and nausea by binding to vagal afferent 5-HT$_3$ receptors. The same mechanism may also release 5-HT in the area postrema (below the fourth ventricle) and trigger the same reflex centrally. Ondansetron is able to interrupt both the central and the peripheral reflex as well as inhibit the emetogenic effect of chemotherapy and radiotherapy by selectively and competitively binding to the 5-HT$_3$ receptor. The exact mechanism of action in post-operative nausea and vomiting is not known.

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 was infused intravenously at doses of 8 mg and 32 mg over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo was 20.0 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.

Pharmacodynamics
The plasma prolactin concentrations are not affected by ondansetron.

Clinical efficacy
See "Pharmacokinetics".

Pharmacokinetics

Absorption
Zofran film-coated tablets, Melt oral lyophilisate and syrup are bioequivalent. The absolute oral bioavailability is 60%. Peak plasma concentrations are attained approximately 1.5 hours after oral administration of 8 mg, and within approximately 20 minutes after IV administration of 0.15 mg/kg over 15 minutes.
The peak active substance concentration varies greatly. There is no direct relationship between the plasma concentrations of the active substance and the anti-emetic effect of the drug.
Following the infusion of 4 mg ondansetron over 5 minutes, the C_{max} is 65 ng/ml.

Distribution
Plasma protein binding is 70 to 76%.

Metabolism
Ondansetron undergoes extensive metabolism in humans, with approximately 5% of a radio-labelled dose detectable as parent compound in the urine. The primary metabolic pathway consists of hydroxylation on the indole ring followed by conjugation with glucuronide or sulphate. Although some non-conjugated metabolic products have pharmacological activity, these compounds can only be found in the plasma at concentrations unlikely to contribute significantly to the biological activity of ondansetron.

It was demonstrated in *in vitro* studies that ondansetron is a substrate of hepatic cytochrome P450 enzymes in humans, including CYP1A2, CYP2D6 and CYP3A4. CYP3A4 is most significant for overall ondansetron turnover. Since ondansetron's metabolism can be carried out by a number of metabolic enzymes, enzyme inhibition or lack of one of the enzymes (e.g. genetic CYP2D6 deficiency) is expected to be compensated by other enzymes and the overall rate of ondansetron elimination is expected to be scarcely affected as a result.
The elimination of ondansetron may be impaired by cytochrome P450-inducing substances. In a pharmacokinetic study with 16 epileptic patients receiving chronic treatment with carbamazepine or phenytoin, lower AUC, C_{max} and $T_{½}$ values were observed for ondansetron. This led to a significant increase in clearance. However, based on the data available, dose adjustment is not recommended (see "Warnings and precautions" and "Interactions").

Elimination
Following IV administration of 10 mg over 10 minutes, ondansetron is almost completely metabolised (73-93%) and is excreted both in the urine (51-63%) and in the faeces (21-31%). Renal excretion is rapid: 44-53% of the dose is excreted in the urine within 24 hours. The main metabolites of renal elimination are conjugates of glucuronic (45%) and sulphuric acid (20%). Less than 5% of the active substance is excreted unchanged in the urine. The half-life for oral and parenteral dosage forms is approx. 3 hours.

Pharmacokinetics in special populations
Children and adolescents (aged 1 month to 17 years)
In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg ondansetron/kg before surgery. In patients aged 1 to 4 months, weight-normalised clearance was reduced by approx. 30% compared to patients aged 5 to 24 months, but comparable to patients aged 3 to 12 years. The half-life in the 1-to-4-month patient population averaged 6.7 hours compared to 2.9 hours for patients in the 5-to-24-month and 3-to-12-year age ranges. Dose adjustment is not required for patients aged 1 to 4 months as only a single IV dose of ondansetron is recommended for treating post-operative nausea and vomiting. The differences in pharmacokinetic parameters can be partially explained by the higher volume of distribution in the 1-to-4-month patient population.
In children aged 3 to 12 years undergoing surgery with general anaesthesia, both the clearance and volume of distribution following a single dose of 2 mg (3 to 7 year olds) or 4 mg (8 to 12 year olds) of ondansetron were markedly reduced in comparison to values for adult patients. Both parameters increased as a function of body weight and, by 12 years of age, were approaching those of young adults. When clearance and volume of distribution were adjusted for body weight, the values for these parameters were similar between the different age groups. Weight-based dosing (0.1 mg/kg to a maximum of 4 mg) can compensate for these changes and normalise systemic exposure in paediatric patients.
A pharmacokinetic analysis was performed in a population of 74 patients aged 6 to 48 months, each receiving three IV doses of 0.15 mg ondansetron/kg 4 hours apart to treat CINV, and in a population of 41 surgical patients aged 1 to 24 months following administration of a single IV dose of 0.1 mg/kg or 0.2 mg ondansetron/kg. The analysis of the pharmacokinetic parameters of the patient population aged 1 to 48 months administered three IV doses of 0.15 mg ondansetron/kg 4 hours apart showed a comparable systemic exposure (AUC) to that of surgical patients aged 5 to 24 months as well as to that observed in earlier studies in paediatric cancer patients (aged 4 to 18 years) and surgical patients (aged 3 to 12 years) given similar dosages.

Elderly patients
Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance and an increase in the 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). There were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in ondansetron CINV clinical studies.
Based on more recent ondansetron plasma concentration measurements and exposure-response modelling, a greater effect on the QTc interval is predicted in patients ≥75 years of age compared to young adults. Specific parenteral dosing recommendations are given for patients over 65 years of age and over 75 years of age (see "Dosage/Administration – CINV and RINV – Elderly patients").

Hepatic impairment
Patients with hepatic impairment have a prolonged elimination half-life (15 to 32 hours), depending on the severity of lesions, markedly reduced systemic clearance and an oral bioavailability approaching 100% due to reduced metabolism.

Pregnancy
No data are available on pharmacokinetics in pregnant women.

Preclinical data

Acute and chronic toxicity
In acute toxicity studies in rats and mice, CNS disorders in the form of behavioural changes were seen at very high dosages. After multiple oral administrations, behavioural changes only occurred in rats and dogs at high dosages. Transient ALT elevations were observed in rats. However, no signs of hepatotoxicity were identified.
As with oral administration, transient behavioural changes were observed following IV administration. Tremor only occurred at high dosages well in excess of human dose ranges (rats: 12 mg ondansetron /kg body weight and dogs 6.75 mg ondansetron /kg body weight)
There was also a transient minor elevation in ALT in rats. Dose-dependent irritation at the injection site was observed in dogs. However, this only occurred at a high concentration of 6.75 mg ondansetron/ml.

Reproductive toxicity
Oral and IV reproductive studies were carried out in rats and rabbits. The studies did not suggest a teratogenic effect of ondansetron. Placental transfer was demonstrated in rats and rabbits.
In embryo-fetal development studies in rats and rabbits pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain, in rabbits there were no significant effects of ondansetron on the maternal animals or the development of the offspring at doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal development toxicity study pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from day 17 to 21 of pregnancy. With the exception of a slight reduction in maternal body weight gain there were no effects on the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At dosages of 15 mg/kg/day in rats the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.
Adverse effects on fertility and post-natal development in rats were not detected. Ondansetron and its metabolites accumulated in rat milk at a milk-plasma ratio of 5.2.

Mutagenicity/carcinogenicity
Mutagenicity and carcinogenicity studies produced no findings relevant to clinical use.

Safety pharmacology
An *in vitro* study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation by blocking hERG potassium channels.
Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see "Properties/Action – QT prolongation").

Other information

General
Zofran ampoules must not be autoclaved.

Compatibility with solutions for infusion
Zofran concentrate for solution for infusion/solution for injection is compatible with the following solutions for infusion: NaCl 0.9%; glucose 5%; mannitol 10%; Ringer's solution; KCl 0.3% + NaCl 0.9% solution; KCl 0.3% + glucose 5% solution.
Preparing the mixtures immediately before use is recommended. The chemical and physical in-use stability is proven for 7 days at room temperature (<25°C), under fluorescent light or refrigerated (2-8°C). For microbiological reasons, the diluted solution should be used as soon as it has been prepared. Discard any leftover solution.
Compatibility tests were performed on infusion bags and the infusion set made of polyvinylchloride.
Diluted solutions of Zofran concentrate for solution for infusion/solution for injection with NaCl 0.9% or glucose 5% are stable in syringes made of polypropylene.

Incompatibilities
Incompatibility with solutions for infusion
Zofran concentrate for solution for infusion/solution for injection should not be mixed with solutions whose physical and chemical compatibility is not proven. This applies in particular to basic solutions as they may form a precipitate.
Note: Mixtures intended to be stored for a longer period of time must be prepared under aseptic conditions.

Compatibility with other medicinal products
Zofran concentrate for solution for infusion/solution for injection must not be mixed with other medicinal products in the same infusion bottle .
However, the substances listed below may be administered using a "Y" adaptor. This is the case for solutions for infusion with a concentration of 16 µg/ml to 160 µg/ml ondansetron (i.e. 8 mg in 500 ml and 8 mg in 50 ml, respectively):

Cisplatin: Concentrations up to 0.48 mg/ml (240 mg in 500 ml) with an infusion time of 1-8 hours.

Carboplatin: Concentrations of 0.18-9.9 mg/ml (90 mg in 500 ml to 990 mg in 100 ml) with an infusion time of 10 minutes to 1 hour.

Etoposide: Concentrations of 0.14-0.25 mg/ml (72 mg in 500 ml to 250 mg in 1 litre) with an infusion time of 30 minutes to 1 hour.

Cyclophosphamide: Aqueous solutions of 100 mg to 1 g (100 mg/5 ml) by IV bolus injection over approx. 5 minutes.

Doxorubicin: Aqueous solutions of 10 to 100 mg (10 mg/5 ml) by IV bolus injection over approx. 5 minutes.

Ceftazidime: Aqueous solutions of 250 mg to 2 g (250 mg/2.5 ml, 500 mg/5 ml, 1 g/10 ml, 2 g/10 ml) by IV bolus injection over approx. 5 minutes.

Dexamethasone: Dexamethasone sodium phosphate 20 mg can be infused over 2-5 minutes using a "Y" adaptor, through which 8 or 32 mg ondansetron, diluted in 50-100 ml of a compatible solution for infusion (see above), is administered over 15 minutes.

Incompatibility with other medicinal products 5-Fluorouracil: Ondansetron should not be mixed with 5-fluorouracil.

Note for diabetics
Zofran syrup is sweetened with sorbitol (35.7 kJ/8.4 kcal per 5 ml), corresponding to 2.1 grams of carbohydrate.

Shelf life
The different dosage forms of Zofran must not be used after the expiry date (= EXP) printed on the pack.
Zofran concentrate for solution for infusion/solution for injection does not contain preservatives and is therefore only designed for single use. The solution must be injected or diluted immediately after opening. Discard any leftover solution.
Mixtures of Zofran concentrate for solution for infusion/solution for injection with the recommended solutions for infusion only have a limited shelf life (see "Other information – Compatibility with solutions for infusion").

Special precautions for storage
Film-coated tablets and Melt oral lyophilisate: Store below 30°C.
Syrup: Store below 30°C in an upright position. Do not store in a refrigerator.
Ampoules: Store at a temperature below 30°C and away from direct light.

Pack sizes

4 mg film-coated tablets: One pack with 10 film-coated tablets
8 mg film-coated tablets: One pack with 10 film-coated tablets, One pack with 6 film-coated tablets
4 mg Melt oral lyophilisate: One pack with 10 Melt oral lyophilisate
8 mg Melt oral lyophilisate: One pack with 10 Melt oral lyophilisate
4 mg/5 ml syrup:50 ml
Ampoules containing concentrate for solution for infusion/solution for injection of 4 mg/2 ml: 5 Ampoules
Ampoules containing 8 mg/4 ml concentrate for solution for infusion: 5 Ampoules
Not all pack sizes and presentations are marketed.

Manufacturer

See folding box.

Information last revised

December 2021

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects 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
Union of Arab Pharmacists