

INSTRUCTION
for medical use

SUSPRIN®

Composition:

active substance: ondansetron;

5 ml of the solution contains ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron;

excipients: citric acid monohydrate; sodium benzoate (E 211); sodium citrate; sorbitol solution, non-crystallizing (E 420); strawberry flavor; purified water.

Pharmaceutical form. Oral solution.

Basic physical and chemical properties: clear liquid with a characteristic odor.

Pharmacotherapeutic group. Antiemetics and antinauseants. Antagonists of serotonin receptors (5HT₃). ATC code A04A A01.

Pharmacological properties.

Pharmacodynamics.

Mechanism of action

Ondansetron is a potent, highly selective antagonist of serotonin receptors (5HT₃). The mechanism of action of ondansetron in nausea and vomiting is not completely determined. Radiotherapy and chemotherapy may cause the release of serotonin (5HT) in the small intestine and initiate the peripheral mechanism of the vomiting reflex by activating vagal afferents via 5HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may cause a release of 5HT in the *area postrema* and, correspondingly, initiate the central mechanism of the vomiting reflex. Thus, ondansetron suppresses nausea and vomiting induced by chemotherapy and radiotherapy due to the antagonism toward 5HT₃ receptors of neurons located both in the peripheral and central nervous system.

The mechanism of action of ondansetron in postoperative nausea and vomiting is not completely determined.

Ondansetron does not alter plasma prolactin concentrations.

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

Pharmacokinetics.

Following oral administration ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first-pass metabolism. Peak plasma concentrations (approximately 30 ng/ml) are attained approximately 1,5 hours after the administration of an 8 mg dose. For doses above 8 mg ondansetron blood concentrations increase disproportionately, as, in this case, its first-pass metabolism may be reduced. Mean bioavailability in healthy male volunteers following administration of a single 8 mg tablet is approximately 55–60%. Bioavailability is somewhat increased when administering the drug with food but is unaffected

by antacids. The distribution of ondansetron is equal following oral, intramuscular and intravenous administration in adults, and is similar to the 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.

Ondansetron is bound to plasma proteins to a moderate extent (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 (sparteine/debrisoquine-type polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeated dosing.

Special patient groups

Gender

The pharmacokinetics of ondansetron depends on the gender of patients. Females demonstrate a greater rate, extent of absorption and a reduced systemic clearance and volume of distribution (adjusted for weight) compared to males.

Children

The differences in pharmacokinetic parameters can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution in children aged 1 to 4 months.

In children aged 3 to 12 the absolute values of ondansetron clearance and distribution volume were reduced in comparison to those in adult patients. Both parameters increased in a linear fashion depending on body weight, and by 12 years of age these values approached those of adult patients.

When clearance and volume of distribution values were normalized 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 systemic exposure in children.

Based on this study, the area under the “concentration-time” curve (AUC) following oral or intravenous administration in children and adolescents was comparable to that in adults, with the exception of infants aged 1 to 4 months. The volume of distribution depended on the age and was lower in adults than in children.

Elderly patients

A greater effect on the QTcF interval is predicted in patients over 75 years of age compared to younger patients.

Renal impairment

In patients with moderate renal impairment (creatinine clearance 15–60 ml/min), both systemic clearance and volume of distribution are reduced after intravenous ondansetron administration, resulting in a slight, clinically insignificant increase in the elimination half-life (5,4 hours). A study in patients with severe renal impairment who required regular hemodialysis showed no changes of ondansetron's pharmacokinetics following intravenous administration.

Hepatic impairment

In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced, with an elimination half-life prolonged up to 15–32 hours, oral bioavailability approaches 100% due to reduced first-pass metabolism.

Clinical characteristics.

Indications.

Adults

Treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Prevention of post-operative nausea and vomiting.

Ondansetron administration by injection is recommended for the treatment of post-operative nausea and vomiting.

Children

Treatment of nausea and vomiting induced by cytotoxic chemotherapy in children aged ≥ 6 months.

There is no study data as to the use of oral ondansetron in children aged over 1 month for the prevention or treatment of post-operative nausea and vomiting, therefore, administration of ondansetron by injection is recommended in this case.

Contraindications.

Concomitant use of ondansetron with apomorphine hydrochloride.

Increased sensitivity to any ingredient of the formulation.

Interactions with other medicinal products and other types of interaction.

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs during co-administration. It has been shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental, or propofol.

Ondansetron is metabolized by multiple hepatic cytochrome P450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolizing ondansetron, 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 effect on overall ondansetron clearance.

Caution should be exercised when co-administering ondansetron with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see section “Administration details”).

Concomitant use of ondansetron and other QT-prolonging medicinal products may cause additional prolongation of this interval.

Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines (doxorubicin, daunorubicin) or trastuzumab), antibiotics (erythromycin), antifungals (ketoconazole), antiarrhythmics (amiodarone) and beta blockers (atenolol or timolol) may increase the risk of arrhythmias (see section “Administration details”).

Serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)).

There is data about the development of the serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) in patients following concomitant use of ondansetron and other serotonergic drugs including SSRIs and SNRIs (see section “Administration details”).

Apomorphine

Concomitant use of ondansetron with apomorphine hydrochloride is contraindicated due to reports of arterial hypotension and loss of consciousness during co-administration.

Phenytoin, carbamazepine and rifampicin

Patients treated with potent inducers of CYP3A4 (for example, phenytoin, carbamazepine and rifampicin) demonstrated an increased clearance of ondansetron (when taken orally) and decreased ondansetron blood concentrations.

Tramadol

Ondansetron may reduce the analgesic effect of tramadol.

Administration details.

Hypersensitivity reactions have been reported in patients who have a history of hypersensitivity to other selective 5HT₃-receptor antagonists. Respiratory disorders should be treated symptomatically, and clinicians should pay particular attention to them as they may be precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see section “Pharmacological properties”). There have been reports of *Torsade de Pointes* in patients using ondansetron. The use of ondansetron should be avoided in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may

develop QT interval prolongation, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT interval prolongation or electrolyte abnormalities.

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be warned about the signs and symptoms of myocardial ischemia.

Hypokalemia and hypomagnesemia should be corrected prior to administration.

There is data about the development of the serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) in patients following the concomitant use of ondansetron and other serotonergic drugs including SSRIs and SNRIs (see section "Interaction with other medicinal products and other types of interaction"). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is known to weaken intestinal peristalsis, patients with signs of intestinal obstruction should be monitored following administration of the drug.

In patients undergoing adenotonsillar surgery, prevention of nausea and vomiting with ondansetron may mask a bleeding. Therefore, such patients should be closely monitored following the administration of ondansetron.

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

The drug contains sorbitol. The energy value of 1 g sorbitol is 2,6 kcal. Sorbitol may have a mild laxative effect. Patients with determined intolerance of some sugars should consult the physician before taking the medicinal product.

This medicinal product contains less than 1 mmol (23 mg)/dose of sodium, i.e. is essentially sodium-free.

Use during pregnancy and breastfeeding.

Women of childbearing age receiving ondansetron should consider the use of contraception.

Pregnancy

Based on 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, the use of ondansetron in the first trimester was associated with an increased risk of oral clefts (3 additional cases per 10000 women treated with ondansetron; adjusted relative risk, 1,24 (95 % CI 1,03-1,48)). The available epidemiological data 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.

Breastfeeding

Experimental studies have shown that ondansetron passes into the milk of lactating animals. Mothers should therefore stop breastfeeding if the administration of the drug is necessary.

Fertility

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

Effect on reaction rate when driving motor transport or using other mechanisms.

Psychomotor tests have revealed that ondansetron does not influence the ability to operate mechanisms, nor does it have a sedative effect. No detrimental effects on such abilities are predicated from the pharmacology of ondansetron.

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 selection of the dose regimen depends on the severity of the emetogenic effect.

Emetogenic chemotherapy and radiotherapy

8 mg of ondansetron (10 ml) taken 1–2 hours before chemotherapy or radiotherapy, followed by 8 mg (10 ml) every 12 hours for a maximum of 5 days.

Highly emetogenic chemotherapy

A single oral dose of 24 mg of ondansetron (30 ml) taken with 12 mg oral dexamethasone sodium phosphate 1–2 hours before chemotherapy.

After the first 24 hours, oral ondansetron is recommended for up to 5 days after the course of treatment.

The recommended dose for oral administration is 8 mg twice daily.

Children

Dose calculation for children over 6 months of age and adolescents up to 17 years of age

The dose of the drug can be calculated based on body surface area or body weight of the child. The total daily dose calculated based on body weight is bigger than the total daily dose calculated based on body surface area.

Dose calculation based on body surface area of child

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m², the intravenous dose must not exceed 8 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (see table 1). The total daily dose of ondansetron (given as divided doses) must not exceed the adult dose of 32 mg.

Table 1

Dose calculation based on body surface area for children over 6 months of age and adolescents up to 17 years of age

Body surface area of child	Day 1 ^(a, b)	Day 2–6 ^(b)
< 0,6 m ²	5 mg/m ² intravenous + syrup at a dose of 2 mg in 12 hours	Syrup at a dose of 2 mg every 12 hours
≥ 0,6 m ² to ≤ 1,2 m ²	5 mg/m ² intravenous + syrup or tablets at a dose of 4 mg in 12 hours	Syrup or tablets at a dose of 4 mg every 12 hours
> 1,2 m ²	5 mg/m ² or 8 mg intravenous + syrup or tablets at a dose of 8 mg in 12 hours	Syrup or tablets at a dose of 8 mg every 12 hours

^a The intravenous dose must not exceed 8 mg.

^b The total daily dose must not exceed the adult dose of 32 mg.

Dose calculation based on body weight of child

The total daily dose calculated based on body weight is bigger than the total daily dose calculated based on body surface area.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0,15 mg/kg. The intravenous dose must not exceed 8 mg. Two further intravenous doses may be given at 4-hour intervals on the first day. Oral administration can commence 12 hours later and may be continued for up to 5 days (see table 2). The total daily dose of ondansetron (given as divided doses) must not exceed the adult dose of 32 mg.

Table 2

Dose calculation based on body weight for children over 6 months of age and adolescents up to 17 years of age

Body weight	Day 1 ^(a, b)	Day 2–6 ^(b)
≤ 10 kg	Up to 3 doses of 0,15 mg/kg every 4	Syrup at a dose of 2 mg every 12 hours

	hours	
> 10 kg	Up to 3 doses of 0,15 mg/kg every 4 hours	Syrup or tablets at a dose of 4 mg every 12 hours

a. The intravenous dose must not exceed 8 mg.

b. The total daily dose must not exceed the adult dose of 32 mg.

Elderly patients

Ondansetron is tolerated well by patients over 65 years of age. No adjustments of dosage or frequency of dosing are required.

Post-operative nausea and vomiting

Adults

16 mg (20 ml) 1 hour prior to anesthesia.

Intravenous ondansetron is used for the treatment of post-operative nausea and vomiting.

Post-operative nausea and vomiting in children over 1 month of age and adolescents under 17 years of age

No studies have been conducted regarding oral administration of ondansetron for prevention or treatment of post-operative nausea and vomiting; for this indication, a slow (no less than 30 seconds) intravenous injection is recommended.

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

Elderly patients

There is limited experience of using ondansetron in the prevention and treatment of post-operative nausea and vomiting in elderly patients, however, ondansetron is tolerated well in patients over 65 years of age receiving chemotherapy.

Patients with renal impairment

No adjustments of the dosing regimen or route of administration are required for patients with renal impairment.

Patients with hepatic impairment

Clearance of ondansetron is significantly reduced and elimination half-life prolonged in patients with moderate and severe impairment of hepatic function. The total daily dose of the drug should not exceed 8 mg in such patients.

Patients with poor sparteine/debrisoquine metabolism

The elimination half-life of ondansetron is not altered in patients with poor sparteine and debrisoquine metabolism. In such patients, repeated dosing gives drug concentrations no different from those in patients with unaffected metabolism. No adjustment of daily dosage or frequency of dosing is therefore required.

Children.

Ondansetron oral solution is indicated for the management of chemotherapy-induced nausea and vomiting in children over 6 months of age.

Intravenous administration of ondansetron is recommended for the prevention or treatment of post-operative nausea and vomiting in children over 1 month of age.

Overdose.

Symptoms.

There is insufficient data as to ondansetron overdose. In most overdose cases the symptoms were similar to adverse reactions that were observed in patients when using recommended doses (see section "Adverse reactions"). Vision disturbances, severe constipation, arterial hypotension and vasovagal episodes with transient 2nd stage atrioventricular blockage were observed in overdoses. Serotonin syndrome was reported to occur in children aged 12 months to 2 years with overdose.

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

Treatment.

There is no specific antidote for ondansetron, therefore, symptomatic and supportive therapy should be used in case of overdose.

The use of ipecacuanha is not recommended because the clinical response to its introduction may be slowed down due to the antiemetic action of ondansetron.

Adverse reactions.

Adverse reactions listed below are classified by organs, systems and frequency. The adverse reactions are classified by frequency as follows: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10000$ и $< 1/1000$), very rare ($< 1/10000$). Very common, common and uncommon adverse reactions were generally determined in clinical trials. Rare and very rare adverse reactions were generally determined during the post-marketing period.

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

Immune system: rare – immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

Nervous system: very common – headache; uncommon – seizures, movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions, and dyskinesia)¹; rare – dizziness during rapid intravenous administration of the drug.

Organs of vision: rare – transient visual disturbances (blurred vision), predominantly during intravenous administration; very rare – transient blindness, predominantly during intravenous administration².

Heart: uncommon – arrhythmia, chest pain (with or without ST segment depression), bradycardia; rare – QT interval prolongation, including ventricular flutter/fibrillation (*torsade de pointes*); frequency unknown – myocardial ischemia (see section “Administration details”).

Vessels: common – sensation of warmth or flushing; uncommon – arterial hypotension.

Respiratory system and thoracic organs: uncommon – hiccups.

Gastrointestinal tract: common – constipation; frequency unknown – dry mouth.

Hepatobiliary system: uncommon – asymptomatic increases in liver function tests.³

Skin and subcutaneous tissue: very rare – toxic skin rashes, including toxic epidermal necrolysis.

¹Observations lack definitive evidence of persistent clinical sequelae.

²Transient blindness resolved within 20 minutes in the majority of cases. Most patients received chemotherapeutic agents which contained cisplatin. There have been some reports of transient cortical blindness.

³These events were mostly observed in patients receiving cisplatin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients and their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the automated pharmacovigilance information system available at: <https://aisf.dec.gov.ua>.

Shelf-life.

2 years.

Storage conditions.

Store at a temperature not more than 25 °C. Do not freeze.

Keep out of reach of children.

Do not use after 28 days of first opening the bottle.

Package.

50 ml are in a bottle. 1 bottle and a measuring device are in a carton package.

Conditions of supply.

By prescription.

Manufacturer.

LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.

40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

or

Manufacturer.

LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.

40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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