APPROVED
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INSTRUCTION
for medical use

SUSPRIN®

Composition:
active substance: ondansetron;
each film-coated tablet contains ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron or ondansetron hydrochloride dehydrate equivalent to 8 mg ondansetron.
excipients: microcrystalline cellulose, lactose anhydrous, partially pregelatinized maize starch, magnesium stearate, coating Opadry 03B51322 green*;
*Opadry 03B51322 green: hypromellose, titanium dioxide (E 171), yellow iron oxide (E 172), polyethylene glycol, indigo carmine (E 132).

Pharmaceutical form. Film-coated tablets.
Basic physical and chemical properties: film-coated green or light-green, round, biconvex tablets, smooth on both sides.

Pharmacotherapeutic group. Antiemetics and antinauseants. Antagonists of serotonin receptors ($5HT_3$). ATC code A04A A01.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Ondansetron is a potent, highly selective antagonist of serotonin receptors ($5HT_3$). 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 $5HT_3$ 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 $5HT_3$ receptors of neurons located both in the peripheral and central nervous system.
The mechanism of action of ondansetron in post-operative nausea and vomiting is not completely determined.
Ondansetron does not affect 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 following 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 patients 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 of the drug 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 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 over 1 month of age 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.

Interaction 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 of the enzymes (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in 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 with 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 (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as 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 the 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 CYP3A4 inducers (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 with a history of hypersensitivity to other selective $5HT_3$-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 lactose. Patients with determined intolerance of some sugars should consult the physician before taking the medicinal product.

Use during pregnancy or 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 on 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
The choice of the dosage regimen is determined by the emetogenicity of cancer treatment.
Adults
Emetogenic chemotherapy and radiotherapy
8 mg of ondansetron taken 1–2 hours before chemotherapy or radiotherapy, followed by 8 mg every 12 hours for a maximum of 5 days.
Highly emetogenic chemotherapy
24 mg of ondansetron taken with 12 mg oral dexamethasone 1–2 hours before chemotherapy.
It is recommended to take 8 mg ondansetron 2 times a day for a maximum of 5 days after the course of treatment to prevent delayed or prolonged emesis after the first 24 hours.
Children under 6 months of age
The dose is calculated based on body surface area or body weight.
Based on body surface area
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. 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 32 mg.

Table 1

Body surface area	Day 1	Days 2-6
< 0,6 m^2	5 mg/m^2 intravenous, then 2 mg* oral in 12 hours	2 mg* oral every 12 hours
≥ 0,6 m^2 and ≤ 1,2 m^2	5 mg/m^2 intravenous, then 4 mg oral in 12 hours	4 mg** oral every 12 hours
> 1,2 м^2	5 mg/m^2 or 8 mg intravenous, then 8 mg oral in 12 hours	8 mg** oral every 12 hours

* ondansetron should be used in the form of an oral solution;
** ondansetron should be used in the form of an oral solution or tablets.

Based on bodyweight
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 of body weight. The intravenous dose must not exceed 8 mg. Two further intravenous doses may be given at 4-hour intervals. 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 32 mg.

Table 2

Bodyweight	Day 1	Days 2-6
≤ 10 kg	up to 3 doses of 0,15 mg/kg intravenous every 4 hours	2 mg* oral every 12 hours
> 10 kg	up to 3 doses of 0,15 mg/kg intravenous every 4 hours	4 mg** oral every 12 hours

* ondansetron should be used in the form of an oral solution;
** ondansetron should be used in the form of an oral solution or tablets.

Elderly patients
There is no need for ondansetron dose adjustment in elderly patients.
Post-operative nausea and vomiting

Adults
16 mg of ondansetron 1 hour prior to anesthesia.
Intravenous ondansetron is used for the treatment of post-operative nausea and vomiting.
Children over 1 month of age
Intravenous ondansetron is recommended for this indication.
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 was tolerated well in patients over 65 years of age receiving chemotherapy.
Patients with renal impairment
No adjustments of daily dosage, frequency of dosing or route of ondansetron administration are required.
Patients with hepatic impairment
Clearance of ondansetron is significantly reduced and elimination half-life prolonged in patients with moderate or severe impairment of hepatic function. The total daily dose 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 required.

Children.
The drug is indicated for use in children over 6 months of age (treatment of chemotherapy-induced nausea and vomiting).
Intravenous administration of ondansetron is recommended for the prevention and 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 observed in patients when using recommended doses (see section "Adverse reactions"). Vision disturbances, severe constipation, arterial hypotension and vasovagal episodes with transient 2nd degree atrioventricular block were observed in overdoses. Serotonin syndrome was reported to occur in children aged 12 months to 2 years.
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 (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10000 и <1/1000), very rare (<1/10000).
Immune system: rare – immediate hypersensitivity reactions, sometimes severe, including anaphylaxis, bronchospasm, urticaria, angioedema, laryngeal edema, stridor, laryngeal spasm.
Nervous system: very common – headache; not common – movement disorders (including extrapyramidal reactions, such as dystonia, oculogyric crisis and dyskinesia)[1]; rare – dizziness, seizures; unknown – weakness, serotonin syndrome, neuroleptic malignant syndrome.
Organs of vision: rare – transient visual disturbances (blurred vision); very rare – transient

blindness[2].
Cardiovascular system: common – sensation of warmth or flushing; uncommon – arrhythmia, bradycardia, arterial hypotension; rare – myocardial infarction, myocardial ischemia, angina pectoris, chest pain (with or without ST segment depression), arrhythmia (including ventricular and supraventricular tachycardia, premature ventricular contraction (extrasystole) and atrial fibrillation), ECG alterations (including heart block, QT interval prolongation and *Torsade de Pointes* arrhythmia), palpitations and syncope; unknown – myocardial ischemia (see section "Administration details").
Respiratory system: uncommon – hiccups.
Gastrointestinal tract: common – constipation, diarrhea; unknown – abdominal pain, dry mouth.
Hepatobiliary system: uncommon – asymptomatic increases of liver function tests[3].
Skin and subcutaneous tissue: uncommon – rash, pruritus; very rare – toxic rashes such as toxic epidermal necrolysis and Stevens-Johnson syndrome.
Metabolic disorders: rare – hypokalemia.
[1]Observations lack definitive evidence of persistent clinical sequelae.
[2]Transient 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.
[3]These 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 continue monitoring the correlation of the benefits and risks related to the use of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions through to the national reporting system and to the applicant through a feedback form at the website: https://kusum.ua/pharmacovigilance/.

Shelf-life.
3 years.

Storage conditions.
Store at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
10 tablets are in a blister. 1 or 3 blisters 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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