APPROVED
Order of the Ministry of Health of Ukraine
15.09.2016 № 973
Registration certificate
№ UA/8976/03/01

INSTRUCTION
for medical use

DOMRID® SR

Composition:
active substance: domperidone maleate;
1 tablet contains domperidone maleate equivalent to domperidone 30 mg;
excipients: lactose monohydrate, povidone, quinoline yellow (E 104), croscarmellose sodium, magnesium stearate, colloidal anhydrous silica, hydroxypropyl methylcellulose, talc.

Pharmaceutical form. Sustained release tablets.
Basic physico-chemical properties: white-yellow, two-layer round plain beveled-edge tablets with "K" logo on the yellow layer of the tablet.

Pharmacotherapeutic group. Propulsives. ATC code A03F A03.

Pharmacological properties.
Pharmacodynamics.
Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. The use of domperidone is very rarely associated with extrapyramidal side effects, especially in adults, however, domperidone promotes the release of prolactin from the pituitary gland. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the *area postrema*.
Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.
Studies in humans have shown oral domperidone to increase lower esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. Domperidone does not affect gastric secretion.
Pharmacokinetics.
Absorption.
Domperidone is rapidly absorbed after oral administration under fasting conditions, with peak plasma concentrations occurring within approximately 60 minutes. The low absolute bioavailability of oral domperidone (approximately 15 %) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in healthy subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15–30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the area under the curve (AUC) somewhat increased when the oral drug is taken after a meal.
Distribution.
Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes (21 ng/ml) after two weeks oral administration of 30 mg per day was almost the same as that after the first dose (18 ng/ml). Domperidone is 91–93% bound to plasma proteins. Distribution studies with the radiolabelled drug in animals have shown wide tissue distribution, but low concentration in the brain. Small amounts of the drug cross the placenta in animals.

Metabolism.
Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation.
In vitro metabolism studies with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in aromatic hydroxylation of domperidone.
Excretion.
Urinary and fecal excretions amount to 31 % and 66 % of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of fecal excretion and approximately 1 % of urinary excretion). The plasma half-life after a single oral dose is 7–9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

Clinical characteristics.
Indications.
Relief of the symptoms of nausea and vomiting.

Contraindications.
Domrid® SR is contraindicated:
- in patients with known hypersensitivity to the active substance or excipients of the drug;
- in patients with prolactin-secretory pituitary tumor (prolactinoma);
- in patients with severe or moderate liver dysfunction (see section «Administration details»);
- in patients with known prolongation of cardiac conduction intervals, particularly the QTc interval, patients with significant electrolyte imbalance or with background heart diseases, such as congestive heart failure (see section «Administration details»);
- when stimulation of gastric motility could be harmful, e.g., in patients with gastro-intestinal hemorrhage, mechanical obstruction or perforation;
- upon concomitant use of ketoconazole, erythromycin or other strong CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section “Interactions with other medicinal products and other types of interaction”);
- upon concomitant use of QT-prolonging medicinal products (at the exception of apomorphine), such as fluconazole, erythromycin, itraconazole, oral ketoconazole, posaconazole, ritonavir, saquinavir, telaprevir, voriconazole, clarithromycin, amiodarone, telithromycin (see sections “Administration details” and “Interaction with other medicinal products and other types of interaction”).

Interaction with other medicinal products and other types of interaction.
Anticholinergic medicinal products may inhibit the anti-dyspeptic effects of domperidone. The risk of QT interval prolongation is increased due to the pharmacodynamic and/or pharmacokinetic interactions.
Antacids or antisecretory agents should not be taken simultaneously with domperidone as they lower its oral bioavailability (see section “Administration details”).
Domperidone is primarily metabolized through CYP3A4. *In vitro* and human data suggest that concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.
Clinically significant changes in the QT interval were observed when domperidone was used concomitantly with potent QT-prolonging CYP3A4 inhibitors. Therefore, concomitant use of domperidone with certain medicinal products is contraindicated (see section “Contraindications”).
Co-administration of levodopa. Although no dosage adjustment of levodopa is deemed necessary, an increase of plasma levodopa concentration (max 30–40 %) has been observed upon co-administration with domperidone (see section “Administration details”).
Concomitant use of the following medicinal products with domperidone is contraindicated.
All QT-prolonging medicinal products (risk of *torsade de pointes*):
- class IA anti-arrhythmics (e.g., disopyramide, quinidine, hydroquinidine);
- class III anti-arrhythmics (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol);
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole);
- certain anti-depressants (e.g., citalopram, escitalopram);

- certain antibiotics (e.g. , levofloxacin, moxifloxacin, erythromycin, spiramycin);
- certain antifungal agents (e.g., fluconazole, pentamidine);
- certain antimalarial agents (e.g., halofantrine, lumefantrine);
- certain gastro-intestinal agents (e.g., cisapride, dolasetron, prucalopride);
- certain antihistamines (e.g., mequitazine, mizolastine);
- certain medicinal products used in cancer (e.g., toremifene, vandetanib, vincamine);
- certain other medicinal products (e.g., bepridil, methadone, diphemanil) (see section "Contraindications");
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled (see section "Contraindications" of the instruction for medical use of apomorphine).

Separate *in vivo* pharmacokinetic / pharmacodynamic interaction studies with concomitant oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4-mediated first pass metabolism by these medicinal products.

With the combination of oral domperidone 10 mg 4 times daily and oral ketoconazole 200 mg 2 times daily, a mean QTc prolongation of 9.8 msec was seen over the observation period; changes at individual time points ranged from 1.2 to 17.5 msec. With the combination of domperidone 10 mg 4 times daily and oral erythromycin 500 mg 3 times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec.

Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. The effect of elevated plasma domperidone concentrations on QTc prolongation is unknown. In these studies, domperidone monotherapy (10 mg given orally 4 times daily) resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200 mg 2 times daily) or erythromycin monotherapy (500 mg 3 times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

Potent CYP3A4 inhibitors not recommended for co-administration with Domrid® SR include:

- azole antifungals, such as fluconazole*, itraconazole, ketoconazole*, posaconazole and voriconazole*;
- macrolide antibiotics, such as clarithromycin*, erythromycin* and telithromycin* (see section "Contraindications");
- protease inhibitors, such as amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, telaprevir*, ritonavir* and saquinavir*;
- calcium antagonists, such as diltiazem and verapamil;
- amiodarone*;
- aprepitant;
- nefazodone.

*Prolong the QTc interval.

Concomitant administration of the following substances requires caution.

Caution should be exercised with bradycardia and hypokalemia-inducing drugs, as well as with QT-prolonging macrolides: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

Caution should be exercised when using domperidone concomitantly with potent CYP3A4 inhibitors that do not prolong the QT interval, such as indinavir. Patients should be closely monitored for signs or symptoms of adverse reactions.

The following list is representative, but not exhaustive.

Domrid® SR may be combined with:

- anti-psychotics the effect of which it increases;
- dopaminergic agonists (bromocriptine, L-dopa), the adverse peripheral effects of which, such as indigestion, nausea, vomiting, it inhibits without neutralizing the basic properties.

As domperidone has a prokinetic effect on the stomach, this may theoretically affect the absorption of concomitantly used oral drugs, particularly sustained release or enteric formulations. However, in patients whose condition has already been stabilized on digoxin or paracetamol, concomitant use of domperidone had no effect on the blood levels of these drugs.

Administration details.
Domrid® SR is not recommended for use in motion sickness.
Domrid® SR should be used with caution in elderly patients or patients with heart disease or history of heart disease.
Cardiovascular effects. Domperidone has been associated with prolongation of the QT interval on the ECG. During post-marketing surveillance, there have been very rare cases of QT prolongation and ventricular flutter-fibrillation in patients taking domperidone. These reports included patients with other risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section "Adverse reactions").
QT interval prolongation observed in healthy volunteers using domperidone at a dose of 80 mg/day (10 or 20 mg 4 times a day) had no clinical significance.
Precautions. Domperidone should be used with caution in patients with mild liver and/or kidney impairment.
Due to increased risk of ventricular arrhythmia, Domrid® SR is contraindicated in patients with prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure (see section "Contraindications"). Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia) and bradycardia are known to be conditions increasing the proarrhythmic risk.
Treatment with Domrid® SR should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patient should consult their physician.
Patients should be advised to promptly report any cardiac symptoms.
Renal impairment. The elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L). Dose reduction may also be required.
Co-administration with levodopa. Although no dosage adjustment of levodopa is deemed necessary, an increase of plasma levodopa concentrations (by 30–40 % at the most) has been observed when domperidone was taken concomitantly (see section "Interaction with other medicinal products and other types of interaction").
Antacids or antisecretory agents should not be taken simultaneously with Domrid® SR as they lower the oral bioavailability of domperidone (see section "Interaction with other medicinal products and other types of interaction"). In case of concomitant administration, the drug Domrid® SR should be taken before meals and antacids or antisecretory agents should be taken after meals.
Use with apomorphine. Domperidone is contraindicated with QT-prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the instruction for medical use of apomorphine are strictly fulfilled.
Use with ketoconazole. Interaction studies with oral ketoconazole have demonstrated QT-interval prolongation. Though the significance of this study has not been determined, alternative treatment should be chosen if antifungal therapy with ketoconazole is indicated (see section "Interaction with other medicinal products and other types of interaction").
The following information on the risk of cardiovascular complications caused by domperidone-containing medicinal products should be taken into account:

- Some epidemiological studies have shown that domperidone may be associated with an increased risk of severe ventricular arrhythmias or a sudden cardiac death (see section "Adverse reactions").
- The risk of serious ventricular arrhythmias or sudden cardiac death may be higher in patients aged 60 and more or with oral use of drug doses over 30 mg per day, as well as in patients concomitantly using QT-prolonging medicinal products or CYP3A4 inhibitors. Therefore, caution is required when using Domrid® SR in elderly patients. Patients aged 60 and more should consult their doctor before using Domrid® SR.
- In adults, domperidone should be administered at the lowest effective dose.

The risk/benefit ratio of the use of domperidone remains favorable.

In case of intolerance to some sugars, consult the physician before using this medicinal product as it contains lactose.
This medicinal product contains less than 1 mmol (23 mg) of sodium/dose, therefore it is essentially sodium-free.

Use during pregnancy or breastfeeding.
Pregnancy.
There are limited post-marketing data on the use of domperidone in pregnant women. Therefore, Domrid® SR should only be used during pregnancy when the anticipated positive effect for the mother overweighs the potential risk for the fetus.
Breastfeeding.
The amount of domperidone that infants may be exposed to through breast milk is extremely low. The maximum relative dose for infants (%) is estimated at approximately 0.1% of the maternal dose, adjusted for body weight. It is not known whether this is harmful to the infant, therefore mothers using Domrid® SR should abstain from breast-feeding.
The decision whether to discontinue breastfeeding or to discontinue domperidone therapy should be made taking into account the benefit of breastfeeding for the child and the benefit of therapy for the mother.
Occurrence of adverse effects, in particular cardiac effects, cannot be excluded after exposure via breast milk. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

Effect on reaction rate when driving motor transport or using other mechanisms.
Dizziness and somnolence have been observed following use of domperidone (see section "Adverse reactions"). Therefore, patients should be advised to abstain from driving motor transport, using other mechanisms or engaging in other activities requiring mental alertness and coordination until they have established how Domrid® SR affects them.

Dosage and administration.
For relief of the symptoms of nausea and vomiting.
Adults. 1 tablet once a day, 15–30 minutes before the meal.
The duration of treatment should not exceed 1 week.
The maximum daily dose of the medicinal product is 30 mg.

Children.
Another pharmaceutical form of the medicinal product should be used in children.

Overdose.
Symptoms. Symptoms of overdose may include agitation, altered consciousness, convulsions, somnolence, disorientation, and extrapyramidal reactions, especially in children.
Treatment. There is no specific antidote to domperidone, but in the event of significant overdose, standard symptomatic treatment should be given immediately. Gastric lavage within 1 hour after the intake of the drug and administration of activated charcoal are recommended, along with close medical supervision and supportive therapy.
ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Anticholinergic, antiparkinsonian drugs may be helpful in controlling the extrapyramidal reactions.

Adverse reactions.
Adverse reactions determined by the results of domperidone use during clinical trials are listed below by organ system and frequency of occurrence: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1000 to <1/100); rare (≥ 1/10000 to <1/1000); very rare (<1/10000). Where the frequency cannot be estimated from clinical trials data, it is recorded as unknown.
Domperidone is normally well tolerated and adverse reactions occur rarely under condition of compliance with the recommendations regarding the dosage and duration of treatment.

Immune system disorders: frequency unknown – allergy reactions, including anaphylaxis, anaphylactic shock, hypersensitivity.
Endocrine system disorders: rare – increased prolactin levels.
Psychiatric disorders: uncommon – decreased libido or loss of libido, nervousness, irritability, agitation; very rare – depression, anxiety.
Nervous system disorders: uncommon – headache, somnolence, dizziness, extrapyramidal disorders; very rare – insomnia, thirst, lethargy, akathisia; frequency unknown – convulsions, restless legs syndrome (exacerbation of restless legs syndrome in patients with Parkinson's disease).
Cardiovascular disorders: very rare – edema, palpitations, heart rate and rhythm disorders, severe ventricular arrythmias; frequency unknown – QT interval prolongation, *"torsade de pointes"* ventricular arrhythmias, sudden cardiac death.
Gastrointestinal disorders: common – dry mouth; uncommon – diarrhea; rare – gastrointestinal disorders, including abdominal pain, regurgitation, change of appetite, nausea, heartburn; very rare – transient intestinal spasms.
Eye disorders: frequency unknown – oculogyric crisis.
Skin and subcutaneous tissue disorders: uncommon – pruritus, rash, urticaria; frequency unknown – angioedema.
Reproductive system and breast disorders: rare – breast enlargement, breast discharge, breast swelling, lactation disorders, irregular menstrual cycle; uncommon – galactorrhea, breast pain, breast tenderness; frequency unknown – gynecomastia, amenorrhea.
Musculoskeletal system and connective tissue disorders: rare – leg pain.
Urinary tract disorders: very rare – dysuria, urinary frequency; frequency unknown – urinary retention.
General disorders: uncommon – asthenia.
Other: conjunctivitis, stomatitis.
Changes in laboratory findings: very rare – elevation of ALT, AST and cholesterol levels; frequency unknown – abnormal liver function tests, elevated blood prolactin levels.
Since the pituitary gland is located outside of the blood-brain barrier, domperidone can increase prolactin levels. In rare cases, such hyperprolactinemia may lead to neuroendocrine adverse reactions such as galactorrhea, gynecomastia and amenorrhea.
During the post-marketing use of the drug, no differences have been noticed in the safety profile of the medicinal product in adults and children, except for extrapyramidal disorders and other phenomena, convulsions and agitation associated with the central nervous system, which were observed mainly in children.
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 in the original package 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 Oblast, Sumy, Skryabina str., 54.

Last revision date.
31.10.2024