APPROVED
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INSTRUCTION
for medical use

DOMRID®

Composition:
active substance: domperidone;
1 ml of suspension contains domperidone 1 mg;
excipients: saccharose, polysorbate 80, colloidal silica anhydrous, sodium carboxymethylcellulose, sodium chloride, propylene glycol, glycerol, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), Ponceau 4R (E 124), strawberry flavor, purified water.

Pharmaceutical form. Oral suspension.
Basic physical and chemical properties: pink suspension with a characteristic odor.

Pharmacotherapeutic group. Propulsives. ATC code A03F A03.

Pharmacological properties.
Pharmacodynamics.
Domperidone is a dopamine antagonist with antiemetic properties. Domperidone slightly penetrates the blood-brain barrier. The use of domperidone is rarely accompanied by extrapyramidal side effects, especially in adults, but domperidone stimulates production of prolactin from the pituitary gland. Its antiemetic effect is possibly due to a combination of peripheral (gastrokinetic) action and antagonism to dopamine receptors in the chemoreceptor trigger zone, which is located outside the blood-brain barrier in the back area (*area postrema*).
Studies in animals, as well as low concentrations that were determined in the brain indicate a predominantly peripheral effect of domperidone on dopamine receptors.
Studies in humans have shown that, when used orally, domperidone increases pressure in the lower esophagus, improves antroduodenal motility and accelerates gastric emptying. Domperidone has no effect on gastric secretion.
Effect on the QT/QTc interval and cardiac electrophysiology.
In accordance with international ICH-E14 guidelines, a thorough study of the QT interval was performed. It was a double-blind placebo-controlled study which involved healthy volunteers taking a dose of up to 80 mg of domperidone per day (10 or 20 mg 4 times a day).
The study revealed that the maximum QTc difference between domperidone (20 mg 4 times a day) and placebo groups was observed on the 4th day of therapy and was 3,4 msec (deviation from the baseline determined by the least squares method). The two-sided 90% upper confidence interval (1,0 to 5,9 msec) did not exceed 10 msec.
This study has not revealed any clinically relevant QTc effects when using domperidone at doses of up to 80 mg a day (that is, more than twice the maximum recommended dosing).
However, two previous studies of drug-drug interaction showed evidence of QTc prolongation when using domperidone as monotherapy (10 mg 4 times a day). The largest mean QTcF difference between domperidone and placebo groups was 5,4 msec (95% confidence interval: 1,7 – 12,4) and 7,5 msec (95 % confidence interval: 0,6 – 14,4) respectively.
Clinical study in children under the age of 12.

A prospective, multicentre, double-blind, randomized, placebo-controlled, parallel-group clinical study was conducted in 292 children aged 6 months to 12 years (median age 7 years) with acute gastroenteritis to evaluate the safety and efficacy of using domperidone. Patients received oral rehydration treatment (ORT) 3 times a day together with a domperidone suspension at 0,25 mg/kg (up to a maximum of 30 mg domperidone a day) or with placebo. The therapy lasted up to 7 days. This study did not reveal greater efficacy (compared to placebo) of combined therapy with the use of domperidone in alleviating the symptoms of vomiting during the first 48 hours of treatment.

Pharmacokinetics.

Absorption.

Domperidone is rapidly absorbed after oral administration in the fasting state, the peak plasma concentration (C_{max}) is reached approximately after 60 minutes. Low absolute bioavailability of oral domperidone (about 15 %) is due to extensive first-pass metabolism in the intestinal wall and in the liver. The C_{max} value and the area under the "concentration-time" curve (AUC) of domperidone increase in proportion to the dose in the 10 mg to 20 mg dose range. A 2- to 3-fold increase of domperidone AUC was observed with repeated administration of domperidone 4 times a day (every 5 hours) for 4 days.

Although in healthy individuals the bioavailability of domperidone is increased when taken after a meal, patients with gastrointestinal complaints should take domperidone 15–30 minutes before the meal. Reduced gastric acidity impairs the absorption of domperidone. Prior concomitant administration of cimetidine and sodium bicarbonate decreases the oral bioavailability of domperidone.

Distribution.

When taken orally, domperidone is not accumulated and does not induce its own metabolism; the peak plasma level after 90 minutes (21 ng/ml) after a two-week oral administration of 30 mg per day was approximately the same as after receiving the first dose (18 ng/ml). Domperidone is 91–93 % bound to the plasma proteins. Studies of domperidone distribution conducted in animals with the use of the radiolabeled drug have shown its significant distribution in the tissues, but low concentration in the brain. In animals, small amounts of the drug cross the placenta.

Metabolism.

Domperidone is rapidly and extensively metabolized in the liver by hydroxylation and N-dealkylation.

In vitro metabolism experiments 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 domperidone aromatic hydroxylation.

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 failure.

Special patient groups.

Hepatic impairment.

In patients with moderate hepatic impairment (7–9 Pugh score, class B according to Child–Pugh classification), the AUC and C_{max} of domperidone were 2,9 and 1,5 times higher, respectively, than in healthy volunteers. The free fraction was increased by 25 %, and the terminal elimination half-life was prolonged from 15 to 23 hours. Patients with mild hepatic impairment demonstrated a somewhat lower exposure than healthy volunteers (based on C_{max} and AUC data) with no change in protein binding or half-life. The use of the drug in patients with severe hepatic impairment was not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see section "Contraindications").

Renal impairment.

In subjects with severe renal impairment (serum creatinine > 6 mg / 100 ml, i.e. > 0,6 mmol/l) the half-life of domperidone was prolonged from 7,4 to 20,8 hours, but plasma drug levels were lower than in patients with normal renal function.

Since a very small amount of the drug (approximately 1 %) is excreted unchanged via the kidneys, it is unlikely that the dose for a single administration in patients with renal insufficiency will need to be adjusted. On repeated administration, the dosing frequency of domperidone should be reduced to 1–2

times a day depending on the severity of the impairment. The dose of the drug may also need to be reduced.

Clinical characteristics.

Indications.

For relief of symptoms of nausea and vomiting.

Contraindications.

Domrid® is contraindicated:

- in patients with known hypersensitivity to domperidone or its excipients;
- in patients with prolactin-secreting pituitary tumor (prolactinoma);
- in patients with moderate to severe hepatic function impairment (see section "Administration details" and "Pharmacological properties");
- in patients with known prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte imbalance and with such underlying cardiac diseases as congestive heart failure (see section "Administration details");
- if stimulation of gastric motility may be dangerous, for instance, in the case of gastrointestinal hemorrhage, mechanical obstruction or perforation;
- in patients with hepatic impairment.

Concomitant use of ketoconazole, erythromycin or other potent CYP3A4 inhibitors is contraindicated (regardless of their ability to prolong the QT interval, see section "Interaction with other medicinal products and other types of interaction").

Concomitant use of drugs that prolong the QT interval (with the exception of apomorphine) such as fluconazole, erythromycin, itraconazole, oral ketoconazole, posaconazole, ritonavir, saquinavir, telaprevir, voriconazole, clarithromycin, amiodarone, telithromycin, is contraindicated (see sections "Interaction with other medicinal products and other types of interaction" and "Administration details").

Interaction with other medicinal products and other types of interaction.

It is not advised to take antacids and antisecretory drugs concomitantly with domperidone since they decrease its bioavailability after oral administration (see section "Administration details"). In case of concomitant use, Domrid® should be administered before meals, and antacids or antisecretory drugs – after meals.

Concomitant use with levodopa.

Even though levodopa dose adjustment is not considered necessary, an increase of plasma levodopa concentrations (by a maximum of 30–40 %) was observed when the drug was administered concurrently with domperidone.

Anticholinergic drugs may neutralize the antidyspeptic effect of domperidone. The risk of QT-interval prolongation is increased due to the pharmacodynamic and/or pharmacokinetic interaction.

Domperidone is metabolized mainly by CYP3A4. According to the data of *in vitro* studies and in humans, concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Concomitant use of domperidone with potent CYP3A4 inhibitors that prolong the QT interval was associated with clinically significant QT interval changes. Concomitant use of domperidone with certain agents is therefore contraindicated (see section "Contraindications").

Concomitant use of the following drugs with domperidone is contraindicated.

All drugs that prolong the QT interval (risk of *torsade de pointes* ventricular tachycardias):

- class IA antiarrhythmics (e.g., disopyramide, quinidine, hydroquinidine);
- class III antiarrhythmics (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol);
- certain neuroleptics (e.g., haloperidol, pimozide, sertindole);
- certain antidepressants (e.g., citalopram, escitalopram);
- certain antibiotics (e.g., levofloxacin, moxifloxacin, erythromycin, spiramycin);
- certain antifungal agents (e.g., fluconazole, pentamidine);
- certain antimalarial agents (in particular halofantrine, lumefantrine);
- certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride);

- certain antihistamines (e.g., mequitazine, mizolastine);
- certain medicines used to treat cancer (e.g., toremifene, vandetanib, vincamine);
- certain other medicines (e.g., bepridil, methadone, diphemanil) (see section "Contraindications");
- apomorphine, unless the benefit of concomitant use outweighs the risks, and only if the recommended precautions for co-administration are strictly followed (see section "Contraindications"). Please consider the recommendations as to the safety of apomorphine use available in its instruction for medical use.

Potent CYP3A4 inhibitors contraindicated for co-administration with Domrid® include:

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

* Prolong the QTc interval.

Concomitant use of the following substances requires caution.

Caution should be exercised when using domperidone with bradycardia and hypokalemia-inducing drugs, as well as with macrolides that may cause QT-interval prolongation: 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 cause QT prolongation, such as indinavir. Patients should be closely monitored for signs or symptoms of adverse reactions. The above list is representative, but not exhaustive.

Domrid® can be combined with:

- antipsychotics, the effect of which it potentiates;
- dopaminergic agonists (bromocriptine, L-dopa) whose undesirable peripheral effects, such as digestive disorders, nausea, vomiting, it inhibits without neutralizing the main properties.

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

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, with changes at individual time points ranging 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 at 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) and erythromycin monotherapy (500 mg 3 times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

Since domperidone has a prokinetic effect on the stomach, it can theoretically affect the absorption of concomitantly used oral medicines, in particular sustained release or enteric-coated dosage forms. However, in patients whose condition has already been stabilized with digoxin or paracetamol, concomitant use of domperidone did not affect the blood levels of these drugs.

Administration details.

Domrid® is not recommended for use in motion sickness.

The drug should be used with caution in elderly patients and in patients with existing cardiac diseases or with a history of cardiac diseases.

Caution. Domperidone should be used with caution in patients with mild hepatic and/or renal impairment.
Renal impairment.
The half-life period of domperidone in severe renal impairment (serum creatinine > 6 mg / 100 ml, i.e. > 0,6 mmol/l) is prolonged. In case of long-term administration, the dosage frequency of domperidone should be reduced to 1–2 times per day depending on the severity of the disorder. In addition, dose reduction might be required.
Cardiovascular effects.
Domperidone was associated with QT-interval prolongation on the ECG. During the post-marketing study, very rare cases of QT prolongation and *torsade de pointes* ventricular tachycardia have been observed in patients taking domperidone. These reports included information about patients with other risk factors, electrolyte disturbances and concomitant treatment, which may have been contributing factors (see section "Adverse reactions"). In accordance with ICH-E14 guidelines, a thorough study of the QT interval was performed in healthy volunteers. QT interval prolongation with domperidone doses of up to 80 mg/day (10 or 20 mg 4 times a day) was clinically insignificant.
Some epidemiological studies revealed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section "Adverse reactions"). The risk of serious ventricular arrhythmias or sudden cardiac death was registered in patients over the age of 60, in patients taking oral doses over 30 mg per day and when using domperidone concomitantly with QT-interval prolonging drugs or CYP3A4 inhibitors.
Domperidone should be administered at the lowest effective dose.
Domperidone is contraindicated in patients with prolonged cardiac conduction intervals, in particular QTc, in patients with significant electrolyte imbalance (hypokalemia, hyperkalemia, hypomagnesemia) or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to an increased risk of ventricular arrhythmia (see section "Contraindications"). Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia) or bradycardia are known as conditions that increase the proarrhythmogenic risk.
In case of signs and symptoms that may be associated with cardiac arrhythmia, the use of the drug Domrid® should be stopped, and the patient should consult the physician immediately.
The patient should be advised about the need to promptly report any cardiovascular symptoms.
It is not advised to take antacids or antisecretory drugs concomitantly with the drug Domrid® since they decrease the bioavailability of domperidone after oral administration (see section "Interaction with other medicinal products and other types of interaction"). In case of concomitant use, the drug Domrid® should be administered before meals, and antacids or antisecretory drugs – after meals.
Concomitant use with apomorphine.
Concomitant use of domperidone is contraindicated with QT-prolonging drugs including apomorphine, unless the benefit of concomitant use outweighs the risks, and only if the recommended precautions for co-administration are strictly followed. Please consider the recommendations as to the safety of apomorphine use available in its instruction for medical use.
Concomitant use with ketoconazole. Prolongation of the QT interval was noted in interaction studies with oral ketoconazole. Although the significance of these data is unclear, an 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 risk/benefit ratio of using domperidone remains favorable.
If you have a known intolerance to some sugars, consult your physician before taking this medicinal product since the drug contains saccharose.
The drug contains the Ponceau 4R dye which may cause allergic reactions. Methyl parahydroxybenzoate and propyl parahydroxybenzoate found in the drug may cause allergic reactions (possibly delayed).

Use during pregnancy or breastfeeding.
Pregnancy.
The post-marketing data on the use of domperidone in pregnant women are limited. Studies in rats have revealed reproductive toxicity in case of administration of high, maternally toxic doses. The potential risk to humans is unknown. Therefore, Domrid® should only be used during pregnancy when, according to the

doctor, the anticipated positive effect for the mother outweighs the potential risk to the fetus.
Breastfeeding.
The amount of domperidone that can penetrate into the organism of the infant through breast milk is estimated at a level below 0.1 % of the mother's dose adjusted for body weight. Occurrence of adverse effects, in particular cardiac effects, cannot be excluded after exposure via breast milk. It is unknown whether the medicinal product can harm the infant, therefore, mothers taking Domrid® should refrain from breastfeeding.
The decision whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy should be made taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
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 (see section "Adverse reactions") have been observed after domperidone use. Therefore, patients should be advised to abstain from driving motor transport, using other mechanisms or performing any activity that requires attention concentration and coordination until they find out how domperidone affects them.

Dosage and administration.
The drug Domrid® should be used at the lowest effective dose for the shortest duration necessary to relieve the symptoms of nausea and vomiting.
Adults and children over the age of 12 and bodyweight over 35 kg: 10 ml of suspension (10 mg) up to 3 times per day.
The maximum daily dose is 30 ml of suspension (30 mg).
It is recommended to take the drug Domrid® orally 15–30 minutes before the meal. If the drug is taken after the meal, absorption of the drug is somewhat delayed.
Patients should try to take each dose of the drug at regular intervals. If the dose is missed, it should not be taken at an uncertain time, the dosing scheme should be followed further. The dose should not be doubled to compensate for the missed one.
The duration of treatment should not exceed 1 week.
Hepatic impairment.
The drug Domrid® is contraindicated in patients with moderate (7–9 points according to the Child – Pugh score) or severe (>9 points according to the Child – Pugh score) hepatic impairment (see section "Contraindications"). Dose adjustment in patients with mild hepatic impairment (5–6 points according to the Child – Pugh score) is not needed (see section "Pharmacological properties").
Renal impairment.
Since domperidone half-life is prolonged in patients with severe renal impairment (serum creatinine > 6 mg / 100 ml, i.e. > 0,6 mmol/l), the frequency of Domrid® administration should be reduced to 1 to 2 times a day depending on the severity of the impairment; dose reduction may also be required. Patients with severe renal impairment should be examined regularly (see sections "Pharmacological properties" and "Administration details").
Children.
The efficacy of domperidone use in children under the age of 12 has not been established (see section "Pharmacological properties"). The efficacy of domperidone use in children over the age of 12 and weighing less than 35 kg has not been established.
Adults > 60 years of age.
Patients over the age of 60 should consult the physician before taking the drug.

Children.
Domrid® should be used at the lowest effective dose for the shortest duration necessary to treat children under the age of 12 and weighing less than 35 kg.

Overdose.

Cases of overdose have been reported, in particular in infants and children.
Symptoms.
The symptoms of overdose may include agitation, impairment of consciousness, muscle cramps, disorientation, somnolence and extrapyramidal reactions.
Treatment.
There is no specific antidote to domperidone. In case of overdose, immediate standard symptomatic treatment is recommended, including: gastric lavage within 1 hour after the intake of the drug, use of activated charcoal, as well as supportive therapy. Careful observation of the patient should be conducted, including ECG monitoring, as the QT interval may be prolonged. Anticholinergic drugs, agents for Parkinson's disease treatment may be effective to control extrapyramidal reactions.

Adverse reactions.
Adverse reactions determined by the results of the use of domperidone in clinical trials are listed below by organ system. The frequency of occurrence is determined as follows: 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 frequency cannot be estimated from clinical trials, it is listed as unknown.
If the recommendations on the dosage and duration of treatment are followed, domperidone is usually well tolerated and adverse reactions are rare.
Immune system: frequency unknown — allergic reactions, including anaphylaxis, anaphylactic shock, hypersensitivity.
Endocrine system: rare — prolactin level increased.
Psychiatric disorders: uncommon — decrease or loss of libido, nervousness, irritability, agitation; very rare — depression, anxiety.
Nervous system: uncommon — headache, somnolence, dizziness, extrapyramidal disorders; very rare — insomnia, thirst, weakness, akathisia; frequency unknown — muscle cramps, restless legs syndrome*.
Organs of vision: frequency unknown — oculogyric crisis.
Cardiovascular system: very rare — edema, palpitation, cardiac arrhythmias, severe ventricular arrhythmias; frequency unknown — QT interval prolongation, *torsade de pointes* ventricular arrhythmias, sudden cardiac death (see section "Administrations details").
Gastrointestinal tract: common — dry mouth; uncommon — diarrhea; rare — gastrointestinal disorders including abdominal pain, regurgitation, change of appetite, nausea, heartburn, constipation; very rare — intermittent intestinal cramps.
Skin and subcutaneous tissue: uncommon — pruritus, rash, urticaria; frequency unknown — angioedema.
Reproductive system and mammary glands: rare — breast enlargement, breast discharge, breast swelling, impaired lactation, irregular menstrual cycle; uncommon — galactorrhea, breast pain, breast tenderness; frequency unknown — gynecomastia, amenorrhea.
Musculoskeletal system and connective tissue: rare — leg pain.
Urinary system: very rare — dysuria, urinary frequency; frequency unknown — urinary retention.
General disorders: uncommon — asthenia.
Other: conjunctivitis, stomatitis.
Changes in laboratory parameters: very rare — increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cholesterol; frequency unknown — abnormal liver function tests, elevated prolactin levels.
* Exacerbation of the restless legs syndrome in patients with Parkinson's disease.

Since the pituitary gland is outside the blood-brain barrier, domperidone may cause an increase in prolactin levels. In rare cases, such hyperprolactinemia may lead to neuroendocrine side effects such as galactorrhea, gynecomastia and amenorrhea.
During the post-marketing use, no differences in the safety profiles of the drug in adults and children have been noted, save for extrapyramidal disorders and other phenomena, seizures and agitation associated with the central nervous system, which were observed mainly in children.
Reporting of suspected adverse reactions.
Reporting 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 or 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. 3 years.
After the first opening of the bottle, store the drug for no more than 3 months.

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

Package.
60 ml or 100 ml are in bottles. Each bottle is in a carton package together with a measuring spoon.

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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