

1. NAME OF THE MEDICINAL PRODUCT

Dompicare 20 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg domperidone.

Excipient with known effect:

Contains 116 mg of lactose.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The film-coated tablets are white, oblong and biconvex with a score line on one face and of about 11.2 mm long and 3.9 mm thick.

The tablets can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

The relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

Adolescents (over 12 years and weighing 35 kg or more)

The relief of the symptoms of nausea and vomiting.

4.2. Posology and method of administration

It is recommended to take this medicine before meals. If taken after meals, absorption of the drug is somewhat delayed.

Adults and adolescents (over 12 years and weighing 35 kg or more)

The initial duration of treatment is four weeks. Patients should be re-evaluated after four weeks and the need for continued treatment re-assessed.

10 mg (1/2 tablet) to 20mg (1 tablet) three to four times per day with a maximum daily dose of 80 mg.

Paediatric population

Dompicare tablets are unsuitable for use in children under 12 years of age and weighing less than 35 kg.

Use in patients with hepatic impairment

No data is available in patients with hepatic impairment. Since domperidone is highly metabolised in the liver, this medicinal product should not be used in patients with hepatic impairment, see section 4.4.

Use in patients with renal impairment

Since very little unchanged drug is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see sections 4.4, 5.2).

4.3. Contraindications

This medicine is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma).

This medicine should not be used when stimulation of the gastric motility could be harmful:

- gastro-intestinal haemorrhage, mechanical obstruction or perforation.

4.4. Special warnings and special precautions for use

Use during lactation:

The total amount of domperidone excreted in human breast milk is expected to be less than 7 µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking this medicine.

Hepatic impairment:

Since domperidone is highly metabolised in the liver, this medicine should not be used in patients with hepatic impairment.

Renal impairment:

In patients with severe renal insufficiency (GFR < 30 ml/min/1.73 m²) the posology should be adjusted (see section 4.2) due to a reduced elimination (see section 5.2).

Cardiovascular effects:

Some epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8.) The risk may be higher in patients older than 60 years or at daily doses of more than 30 mg. Domperidone should be used at the lowest effective dose in adults and children.

Use of domperidone and other drugs which prolong QTc intervals requires that caution be exercised in patients who have existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

Drug interactions

Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided.

Data regarding the effect of domperidone on other drugs' metabolism is lacking. Therefore, concomitant use of domperidone and drugs with narrow therapeutic windows should be performed with caution.

For further interactions, please see section 4.5 "Interaction with other medicinal products and other forms of interaction".

Precautions for use:

The film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5. Interaction with other medicinal products and other forms of interaction**Effects of other drugs on domperidone**

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

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.

The results of this interaction study should be taken into account when prescribing domperidone concomitantly with strong CYP3A4 inhibitors. Strong CYP3A4 inhibitors include: ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, telithromycin, erythromycin, ketoconazole, itraconazole and nefazodone (see section 4.4 Special warnings and special precautions for use).

Systemic exposure of domperidone can be reduced by inducers of CYP3A4 such as rifampicin, carbamazepine, efavirenz and St. John's wort.

In vitro and animal *in vivo* studies suggest a potential risk of domperidone crossing the blood-brain barrier, when co-administered with substances, which are inhibitors of P-glycoprotein. The potential risk in humans is unknown. Nonetheless, concomitant use of domperidone and drugs, which are P-glycoprotein inhibitors (e.g. verapamil, quinidine, ketoconazole and clarithromycin) should be performed with caution.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice 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 10mg four times daily and oral erythromycin 500mg three 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. In these

studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) and erythromycin in monotherapy (500 mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of drugs that reduce gastric acidity, e.g. proton pump inhibitors, H2 receptor antagonists, and antacids.

Effects of domperidone on other drugs

Because of its pharmacologic effects on transit time in the stomach and small intestine, domperidone may alter the absorption of certain drugs. The extent of absorption of drugs that disintegrate, dissolve, and/or are absorbed mainly in the stomach (e.g., digoxin) may be diminished by domperidone, whereas the rate and extent of absorption of drugs that are mainly absorbed in the small intestine (e.g. acetaminophen, aspirin, cyclosporine, diazepam, ethanol, levodopa, lithium, tetracycline) may be enhanced. The clinical importance of these effects has not been determined.

Data regarding the effect of domperidone on other drugs' metabolism is lacking. Therefore, concomitant use of domperidone and drugs with narrow therapeutic windows should be performed with caution.

4.6. Fertility, pregnancy and lactation

Fertility

There are no data on the effects of domperidone on human fertility.

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, this medicine should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactation

The drug is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800 ng/ml after oral and i.v. administration of 2.5 mg/kg respectively). Domperidone concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations and expected not to exceed 10ng/ml. The total amount of domperidone excreted in human breast milk is expected to be less than 7 µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking this medicine.

4.7. Effects on ability to drive and use machines

This medicine has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

The following frequencies are used for the description of the occurrence of adverse reactions:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Class	Organ	Adverse Drug Reaction Frequency		
		Rare	Very Rare	Unknown
Immune disorders	system		Anaphylactic reactions including anaphylactic shock Angioedema Allergic reaction	
Endocrine disorders		Increased prolactin levels		
Psychiatric disorders			Agitation Nervousness	
Nervous disorders	system		Extrapyramidal side effects Convulsions Somnolence Headache	
Cardiac disorders				QTc prolongation Ventricular arrhythmias Sudden cardiac death
Gastrointestinal disorders		Gastrointestinal disorders, including very rare transient intestinal cramps	Diarrhoea	
Skin and subcutaneous tissue disorders			Urticaria Pruritus Rash	
Reproductive system and breast disorders		Galactorrhoea Gynaecomastia Amenorrhoea		
Investigations			Liver function test abnormal	

As the hypophysis is outside the blood brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea.

Extrapyramidal side effects are very rare in neonates and infants, and exceptional in adults. These side effects reverse spontaneously and completely as soon as the treatment is stopped.

Other central nervous system-related effects of convulsion, agitation and somnolence also are very rare and primarily reported in infants and children.

4.9. Overdose

Symptoms

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone, but in the event of overdose, gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. 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 man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

5.2. Pharmacokinetic properties

Absorption

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 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 normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. The time of peak absorption is slightly delayed and the 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 of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. In humans, the apparent volume of distribution is 5.7 L/kg, after intravenous administration. Domperidone is 91-93% bound to plasma proteins.

Biotransformation

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation. The domperidone metabolites are pharmacologically inactive.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects.

Special populations

Hepatic impairment

No pharmacokinetic studies in patients with hepatic impairment are available. Domperidone is eliminated mainly by metabolism and therefore, caution is recommended in patients with hepatic impairment, see sections 4.2, 4.4.

Renal impairment

In patients with severe renal impairment (GFR <30 ml/min/1.73 m²) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers, see sections 4.2, 4.4.

5.3. Preclinical safety data

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In *in vitro* experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 5- and 30-fold, based on IC₅₀ values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 20mg (q.i.d.). Exposure margins for prolongation of action potential duration in *in vitro* experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (20mg q.i.d) by 17-fold. However, safety margins in *in vitro* pro-arrhythmic models (isolated Langendorff perfused heart) and in *in vivo* models (dog, guinea pig, rabbits sensitised for Torsade de pointes) exceeded the free plasma concentrations in humans at maximum daily dose (20mg q.i.d.) by more than 17-fold. In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 10-fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core:

Lactose monohydrate
Povidone
Maize starch
Crospovidone
Sodium laurilsulfate
Microcrystalline cellulose
Hydrogenated castor oil
Magnesium stearate

Coating:

Hypromellose

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and content of container

Blister packs consisting of PVC/Aluminium.

Pack sizes of 10, 20, 30, 40, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for use and handling, and disposal (if appropriate)

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 April 2013

10. DATE OF REVISION OF THE TEXT

17/04/2013