Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Domperidone Pierre Fabre 10mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One orodispersible tablet contains domperidone 10 mg.

Excipient : sulphur dioxide.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet.

Uniformly white or almost white, biconvex, round orodispersible tablet with a characteristic odor of mint.

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.

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

Adults and adolescents (over 12 years and weighing 35 kg or more)
1 to 2 of the 10 mg tablets three to four times per day with a maximum daily dose of 80 mg. (see section 4.4)

Since the tablet dissolves rapidly in the mouth with the help of the saliva, the orodispersible tablet can be taken with or without water.
Without water, place the tablet on the tongue and let it dissolve in the mouth before swallowing. If convenient, a glass of water can be taken afterwards.
The tablet can be also dispersed into a glass of water immediately before swallowing.

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

For children weighing less than 35 kg, other domperidone containing products are available.

Additional information on special populations

Use in patients with liver insufficiency
Since domperidone is highly metabolised in the liver, this medicine should be used with caution in patients with hepatic impairment, see section 4.4.

Use in patients with renal insufficiency
Given the renal excretion of domperidone, and in case of prolonged therapy, the dose of the medicine should be reduced to once or twice daily in patients with renal insufficiency. Moreover, 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 digestive perforation.

4.4 Special warnings and 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 this medicine is not recommended in breast-feeding women.

Use in liver disorders
Since domperidone is highly metabolised in the liver, caution is recommended in patients with hepatic impairment. (see sections 4.2, 5.2).

Renal insufficiency
In patients with severe renal insufficiency (serum creatinine > 6 mg/100 mL, i.e. > 0.6mmol/L), the posology should be adjusted (see section 4.2) due to a reduced elimination (see section 5.2). Such patients on prolonged therapy should be reviewed regularly.

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 30mg. 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.

Use with potent CYP3A4 inhibitors
Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided (see section 4.5 interaction with other medicinal products and other forms of interaction).

Use in infants and children
Neurological side effects are rare (see section 4.8)
Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children. Therefore, it is recommended that the dose be determined accurately and followed strictly in neonates, infants, toddlers and small children .
Overdosing may cause extrapyramidal symptoms in infants and children, but other causes should be taken into consideration.

This medicinal product contains sulphur dioxide. The sulphur dioxide may rarely cause severe hypersensitivity

reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

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 CYP3 A4 mediated first pass metabolism by these drugs.

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 Cmax 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 monotherapy (500mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). The potential risk for humans is unknown. Therefore, this medicine should only be used during pregnancy when justified by the anticipated therapeutic benefit.

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 7µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore this medicine is not recommended in breast-feeding women.

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 adverse drug reactions are ranked below by frequency, using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, < 1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class (MedDRA classification)	Rare (≥1/10,000, <1/1,000),	Very rare (<1/10,000),	Not known (cannot be estimated from the available data)
Immune System Disorder:		allergic reactions including anaphylaxis, anaphylactic shock, anaphylactic	

		reaction and angioedema	
Endocrine disorder:	increased prolactin levels[1].		
Psychiatric system disorders		Agitation[3], nervousness	
Nervous system disorders		extrapyramidal side effects[2], convulsion[3], somnolence[3], headache	
Gastrointestinal disorders:	gastro-intestinal disorders, including very rare transient intestinal cramps;	diarrhoea.	
Skin and subcutaneous tissue disorders		urticaria, pruritus, rash.	
Reproductive system and breast disorders:	galactorrhoea, gynaecomastia, amenorrhea.		
Cardiac disorders:			QTc prolongation Ventricular arrythmias and sudden cardiac death (see section 4.4)
Investigations		liver function test abnormal	

[1]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.

[2]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.

[3]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

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions, especially in children.

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 oesophaegeal 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. 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 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. Domperidone is 91-93% bound to plasma proteins. .

Metabolism
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.

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 but is prolonged in patients with severe renal insufficiency.

Special patient groups
Liver 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 insufficiency (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L) 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.

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 section 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 20 mg (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 torsades de points) exceeded the free plasma concentrations in humans at maximum daily dose (20 mg 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.

Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration.
Small amounts of drug cross the placenta in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Mannitol,
Maltodextrin
Croscarmellose, sodium
Cellulose, microcrystalline
Magnesium stearate
Acesulfame potassium

Flavouring agent:
Peppermint flavour powder n° SN 13627517 (essential oil of star anise, clove oil, essential oil of corn mint, peppermint oil, L-menthol, maltodextrin, arabic gum, sulphur dioxide), ammonium glycyrrhizate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

10 or 30 orodispersible tablets in heat-formed blister packs (PVC/PE/PVDC/Aluminum).
30 orodispersible tablets in heat-formed blister packs (PVC/PE/PVDC/Aluminum).

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1287/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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