SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report side effects.

1. NAME OF THE MEDICINAL PRODUCT

Dismotil 10mg Tablets or
Domperidone 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Domperidone maleate equivalent to 10mg domperidone base

Excipient(s) with known effect:
Lactose monohydrate: 54.200 mg/tablet
Sodium: 0.012 mg/tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, round, biconvex tablets marked “Dm 10” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Domperidone Tablets are indicated for the relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

Domperidone Tablets should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.

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

Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be

doubled to make up for a missed dose.

Usually, the maximum treatment duration should not exceed one week.

Adults and adolescents (12 years of age and older and weighing 35kg or more):
One 10mg tablet up to three times per day with a maximum dose of 30mg per day.

Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35kg:
Due to the need for accurate dosing, Domperidone tablets, are unsuitable for use in children and adolescents weighing less than 35kg.

Hepatic Impairment
Domperidone Tablets are contraindicated in moderate or severe hepatic impairment (see section 4.3). Dose modification in mild hepatic impairment is however, not needed (see section 5.2).

Renal Impairment
Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of Domperidone Tablets should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced.

4.3 Contraindications

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Patients with a prolactin-releasing pituitary tumour (prolactinoma).
- Domperidone should not be used when stimulation of the gastric motility could be harmful: gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see section 5.2).
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac disease such as congestive heart failure (see section 4.4).
- Co-administration with QT-prolonging drugs, at the exception of apomorphine (see sections 4.4 and 4.5).
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section 4.5).

4.4 Special warnings and precautions for use

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

The tablets contain sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Cardiovascular effects
Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section 4.8).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and children.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section 4.3).

Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine

Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the coadministration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the apomorphine SmPC are strictly fulfilled. Please refer to the apomorphine SmPC.

Use in infants
Although neurological side effects are rare (see section 4.8), the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life.
Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

Renal impairment:
The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

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 10mg four times daily and ketoconazole 200 mg 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 10 mg four times daily and oral erythromycin 500 mg 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 10 mg 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 (200 mg twice daily) and erythromycin monotherapy (500 mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated

QTc-prolonging medicinal products:

- anti-arrhythmics class 1A (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain antipsychotics (e.g., haloperidol, pimozide, sertindole)
- certain antidepressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) (see section 4.3).
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SmPC.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:

- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin and telithromycin)

(see section 4.3).

Concomitant use of the following substances is not recommended
Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.
(see section 4.3).

Concomitant use of the following substances requires caution in use
Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

There is a theoretical potential that domperidone may antagonise the hypoprolactinaemia effect of drugs such as bromocriptine.

Opioid analgesics and antimuscarinics may antagonise the prokinetic effects of domperidone.

4.6 Fertility, pregnancy and lactation

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, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding
Domperidone is excreted in human milk and breast-fed infants receive less than 0.1% of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy 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.

4.7 Effects on ability to drive and use machines

No or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions:
The safety of domperidone was evaluated in clinical trials and in post-marketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double blind, placebo controlled studies. All patients were at least 15 years old and received at least one dose of domperidone base. The median total daily dose was 30 mg (range 10 to 80 mg),

and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or Parkinsonism were excluded.

The following headings are used to organise the undesirable effects in order of decreasing frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	**Adverse Drug Reaction Frequency**				
	Common	**Rare**	**Uncommon**	**Very rare**	**Not known**
Immune system disorders					Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders			Loss of libido, Anxiety		Agitation, Nervousness
Nervous system disorders			Somnolence, Headache		Convulsion, Extrapyramidal disorder
Eye disorders					Oculogyric crisis
Cardiac disorders					Ventricular arrhythmias, Sudden cardiac death, QTc prolongation, Torsade de Pointes (see section 4.4)
Gastrointestinal disorders	Dry mouth		Diarrhoea		
Skin and subcutaneous tissue disorder			Rash, Pruritus		Urticaria, Angioedema
Renal and urinary disorders					Urinary retention
Reproductive system and breast disorders			Galactorrhoea, Breast pain, Breast tenderness		Gynaecomastia Amenorrhoea
General disorders and administration site conditions			Asthenia		
Investigations					Liver function test abnormal Blood prolactin increased

In 45 studies where domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart

from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

Paediatric population:
Extrapyramidal disorder occurs primarily in neonates and infants. Other central nervous system related effects of convulsion and agitation also are primarily reported in infants and children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is recommended. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Mechanism of action
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.

In accordance with ICH-E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80mg per day, 10 or 20mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20mg domperidone administered 4 times a day on Day 4. The 2-sided 90% CI (1.0 to 5.9 msec) did not exceed 10msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10mg 4 times a day). The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4msec (95 % Cl: -1.7 to 12.4) and 7.5msec (95% Cl: 0.6 to 14.4), respectively.

5.2 Pharmacokinetic properties

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hr after dosing. The Cmax and AUC values of domperidone increased proportionally with dose in the 10mg to 20mg dose range. A 2-to-3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

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 21ng/ml after two weeks oral administration of 30mg per day was almost the same as that of 18ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. 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.

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.

Hepatic impairment
In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax of domperidone is 2.9- and 1.5- fold higher, respectively, than in healthy subjects.

The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on Cmax and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Renal impairment
In subjects with severe renal insufficiency (creatinine clearance <30 ml/min/1.73m^2) 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 (approximately 1%) 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.

Paediatric population
No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QTc interval in humans. In *in vitro* experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26-47-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 10mg administered 3 times a day. Safety 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 (10 mg administered 3 times a day) by 45-fold. Safety margins in *in vitro* pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45- fold. In *in vivo* models the no effect levels for

QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anaesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain. In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-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

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Povidone
Magnesium stearate
Colloidal anhydrous silica
Sodium lauryl sulphate/Sodium Laurilsulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package

6.5 Nature and contents of container

Blister packs consisting of aluminium and PVC.
Pack sizes of 10, 30, 50 or 100 tablets

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd.
Unit 4, Metro Centre,
Tolpits Lane,
Watford,
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WD18 9SS
Trading as: Co-Pharma

8. MARKETING AUTHORISATION NUMBER(S)

13606/0090

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14/6/02

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