Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Domerid 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg domperidone (as domperidone maleate).
Excipient(s)with known effect
Each tablet contains 51.49 mg lactose (as lactose monohydrate) and 0.012 mg (0.00052 mmol) sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, biconvex tablet with inscription “Dm10” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Domperidone is indicated for the relief of the symptoms of nausea and vomiting. Domperidone is used in adults and adolescents over 12 years and with a body weight of 35 kg or more.

4.2 Posology and method of administration

Posology

Domperidone 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 medicinal product 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 35 kg or more):
One 10 mg tablet up to three times per day with a maximum dose of 30 mg per day.

Paediatric population
The efficacy of domperidone has not been established in children under 12 years and adolescents aged 12 years or more with a body weight under 35 kg (see section 5.1).

Special populations
Hepatic impairment
Domperidone is 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 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:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- prolactin-releasing pituitary tumour (prolactinoma)
- when stimulation of the gastric motility could be harmful, e.g., in patients with 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 diseases such as congestive heart failure (see section 4.4)
- co-administration with QT-prolonging medicinal products, with 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

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

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 medicinal products or CYP3A4 inhibitors.

Use with apomorphine:
Domperidone is contra-indicated with QT prolonging active substances 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 apomorphine SmPC are strictly fulfilled. Please refer to the apomorphine SmPC.

Domperidone should be used at the lowest effective dose.

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.

Paediatric population
Although neurological adverse events are rare (see section 4.8), the risk of neurological adverse events is higher in children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life.

Overdosing may cause extrapyramidal disorders in children.

Excipients
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

When antacids or antisecretory medicinal products are used concomitantly, they should not be taken simultaneously with oral formulations of domperidone, i.e., they should be taken after meals and not before meals.

Co-administration with levodopa:
Although no dose adjustment of levodopa is deemed necessary, an increase (maximum of 30% - 40%) of plasma concentration has been observed when domperidone was taken concomitantly with levodopa.

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

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 (risk of torsades de pointes)
- anti-arrhythmics class IA (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., levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., fluconazole, pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicinal products (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicinal products used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicinal products (e.g., bepridil, diphemanil, methadone)
- 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.
(see section 4.3).

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:
- protease inhibitors (e.g., ritonavir, saquinavir, telaprevir)
- systemic azole antifungals (e.g., itraconazole, ketoconazole, posaconazole, voriconazole)
- certain macrolide antibiotics (e.g., 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.

Concomitant use of the following substances requires caution with use

Caution with bradycardia and hypokalaemia-inducing active substances, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

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 events, 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

Dizziness and somnolence have been observed following use of domperidone (see section 4.8). Therefore, patients should be advised not to drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how domperidone affects them.

4.8 Undesirable effects

The safety of domperidone was evaluated in clinical trials and in post-marketing experience. The clinical trials included 1,275 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. 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 terms and frequencies are applied: *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). Where frequency can not be estimated from clinical trials data, it is recorded as Not known.

System Organ Class	**Adverse Reaction Frequency**		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety Agitation Nervousness	
Nervous system disorders		Dizziness Somnolence Headache Extrapyramidal disorder	Convulsion Restless legs syndrome*
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias QTc prolongation Torsade de Pointes Sudden cardiac death (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

*exacerbation of restless legs syndrome in patients with Parkinson's disease

In 45 clinical studies where domperidone was used at higher doses, 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

Treatment
There is no specific antidote to domperidone. In the event of overdose, standard symptomatic treatment should be given immediately. ECG monitoring should be undertaken, because of the possibility of QTc interval prolongation. Gastric lavage as well as the administration of activated charcoal may be useful. Close medical supervision and supportive therapy is recommended.
Anticholinergic, anti-parkinson medicinal products may be helpful in controlling the extrapyramidal disorders.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, propulsives
ATC code: A03 FA03

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 adverse events 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 80 mg per day (10 or 20 mg administered four 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 20 mg domperidone administered four times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/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 given as monotherapy (10 mg administered four times a day).The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

A clinical study in children ≤ 12 years old

A multicenter, double-blind, randomised, placebo-controlled, prospective study with a parallel group design was conducted to assess the safety and efficacy of domperidone in 292 children with acute gastroenteritis in the age from 6 months to 12 years (median age 7 years). In addition to oral rehydration therapy (ORT), the subjects were randomly given either 0.25 mg/kg domperidone as an oral suspension (up to a maximum of 30 mg domperidone per day) or placebo, three times per day for up to 7 consecutive days. This study did not reach its primary aim, that was to show that domperidone oral suspension plus ORT is more effective than placebo plus ORT in reducing the number of vomiting episodes in the first 48 hours after starting the treatment (see section 4.2).

5.2 Pharmacokinetic properties

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

Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastrointestinal complaints should take domperidone 15 to 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 domperidone is taken after a meal.

Distribution
Domperidone is 91–93% bound to plasma proteins. Distribution studies with radio-labelled active substance in animals have shown wide tissue distribution, but low brain concentration. Small amounts of active substance cross the placenta in rats.

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.

Elimination
Urinary and faecal excretions amount to 31% and 66% of the oral dose respectively. The proportion of the active substance 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 C_{max} 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 C_{max} 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 impairment (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 active substance levels were lower than in healthy volunteers.
Since very little unchanged active substance (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 impairment.
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 10 mg administered three 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 three times a day) by 45-fold. Safety margins in *in vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three 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 (10 mg administered three times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized 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 (10 mg administered three 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

Microcrystalline cellulose
Lactose monohydrate
Maize starch
Magnesium stearate
Povidone K30
Sodium laurylsulfate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 ºC.
Store in the original package, in order to protect from light.

6.5 Nature and contents of container

Blister packs consisting of PVC and aluminium foil.
Pack size: 10, 20, 30, 50 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown

Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/046/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04th April 2003
Date of last renewal: 08th October 2007

10 DATE OF REVISION OF THE TEXT

May 2020