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Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ridonex 10 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg domperidone.

Excipient with known effect:

Contains sulphur dioxide (E220) and maltodextrin (source of glucose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablets. White tablet round with 5 mm of diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Domperidone is 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 tablets 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.

Posology:

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

One 10 mg tablet up to three times a day with a maximum dose of 30 mg per day.

Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg

Due to the need for accurate dosing, tablets, effervescent granules and suppositories are unsuitable for use in children and adolescents weighing less than 35 kg.

Hepatic Impairment

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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. Patients with severe renal impairment should be reviewed regularly (see section 5.2).

Method of administration:

For oral administration.

The orodispersible tablet dissolves rapidly in the mouth with the help of the saliva, and the can be taken with or without water. When taken without water, the tablet should be placed on the tongue and dissolve in the mouth before swallowing. If convenient, a glass of water can be taken afterwards.

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 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

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.

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

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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 proarrhythmic risk.

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

Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine:

Domperidone is contraindicated with QT prolonging drugs 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.

Excipients

The excipient sulphur dioxide (E220) may rarely cause severe hypersensitivity reactions and bronchospasm.

The excipient maltodextrin contains source of glucose. Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptic effect of 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.

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

Concomitant use of the following substances is contraindicated

All QTc-prolonging medicinal products (risk of torsades de points)

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)

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- 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., fluconazole, 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)
- 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 (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 QTinterval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated 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, this medicine 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.

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Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effectsSummary of the safety profile

The safety of domperidone was evaluated in 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GERD), 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 (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.

Tabulated list of adverse reactions

The following terms and frequencies are applied: 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 ($< 1/10,000$).

Where frequency cannot be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	Adverse Drug 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		Somnolence, Headache Extrapyramidal disorder	Convulsion
Eye disorders			Oculogyric crisis
Cardiac disorders (see section 4.4)			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

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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

Paediatric population

In postmarketing experience, there were no differences in the safety profile of adults and children with the exception of extrapyramidal disorders which occurred primarily in neonates and infants (up to one year of age).

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

An increase in the risk of serious ventricular arrhythmias has been reported in some epidemiology studies.

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 OverdoseSymptoms

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

Treatment

In the event of overdose, standard symptomatic treatment should be given immediately. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. There is no specific antidote to domperidone; but in the event of a large overdose, gastric lavage within one hour of ingestion as well as the administration of activated charcoal may be useful. Close medical supervision and supportive therapy are recommended.

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

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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.

Clinical efficacy and safety

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 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 20 mg domperidone administered 4 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 administered as monotherapy (10 mg 4 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.

5.2 Pharmacokinetic propertiesAbsorption

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 hr) dosing of domperidone for 4 days.

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.

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.

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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.

Elimination

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 populations

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 insufficiency (creatinine clearance < 30 ml/min/1.73m²) 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 is available for 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 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

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administered 3 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 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 (10 mg administered 3 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 at in humans at maximum daily dose (10 mg 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

Microcrystalline cellulose

Crospovidone

Lemon flavour*

Magnesium stearate

Saccharin sodium

Sodium laurylsulfate

Hydrophobic colloidal silica

*Lemon flavour is composed of: maltodextrin (source of glucose), gum acacia, butylated hydroxy-anisole, sulphur dioxide (E220), alpha-pinene, beta-pinene, myrcene, limonene, gamma-terpinene, neral and geranial.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

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6.5 Nature and contents of container

Pack sizes of 10, 20, and 30 tablets.

Blister packs consisting of PVC-PVDC/Aluminum.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd

Clonmel

Co. Tipperary

Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/291/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th September 2016

10 DATE OF REVISION OF THE TEXT

June 2019