# 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:
Each orodispersible tablet contains < 10 ppm 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

Ridonex is indicated for the relief of the symptoms of nausea and vomiting.Ridonex is indicated in adults and adolescents aged 12 years and older and weighing 35 kg or more.

### 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 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 in children less than 12 years of age has not been established (see section 5.1).
The efficacy of domperidone in adolescents 12 years of age and older and weighing less than 35 kg has not been established.

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.

Method of administration:
For oral administration.

The orodispersible tablet dissolves rapidly in the mouth with the help of the saliva, and 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, e.g. in patients with gastrointestinal 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 drugs, 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 drugs or CYP3A4 inhibitors.

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 proarrhythmic 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 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.

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 interaction**

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.

*Co-administration with levodopa*
Although no dosage 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 drugs 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 points)

- 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. , erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., fluconazole, pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastrointestinal 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 (e.g., 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 in use**
Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval 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.

**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 this medicines affects them.

**4.8 Undesirable effects**

Summary of the safety profile
The safety of domperidone was evaluated in clinical trials and in post-marketing experience. The clinical trials included 1,275 patients with dyspepsia, gastroesophageal 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 (≥ 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 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<br>Anxiety<br>Agitation<br>Nervousness | |
| ***Nervous system disorders*** | | Dizziness<br>Somnolence<br>Headache<br>Extrapyramidal disorder | Convulsion<br>Restless legs syndrome * |
| ***Eye disorders*** | | | Oculogyric crisis |
| ***Cardiac disorders*** | | | Ventricular arrhythmias<br>QTc-prolongation<br>Torsade de Pointes<br>Sudden |

| | | | |
|---|---|---|---|
| | | | cardiac death (see section 4.4) |
| ***Gastrointestinal disorders*** | Dry mouth | Diarrhoea | |
| ***Skin and subcutaneous tissue disorder*** | | Rash<br>Pruritus<br>Urticaria | Angioedema |
| ***Renal and urinary disorders*** | | | Urinary retention |
| ***Reproductive system and breast disorders*** | | Galactorrhoea<br>Breast pain<br>Breast tenderness | Gynaecomastia<br>Amenorrhoea |
| ***General disorders and administration site conditions*** | | Asthenia | |
| ***Investigations*** | | | Liver function test abnormal<br>Blood prolactin increased |

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

In 45 clinical 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.

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

**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. 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. Close medical supervision and supportive therapy is recommended. Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal disorders.

It is advisable to contact a poison control centre to obtain the latest recommendations for the management of an overdose.

**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 disorders 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 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 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.

Clinical study in infants and children 12 years of age and younger
A multicentre, double-blind, randomised, placebo-controlled, parallel-group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomised subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing vomiting episodes during the first 48 hours after the first treatment administration (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 hr) 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 – 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
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.

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 impairment (creatinine clearance < 30 ml/min/1.73 $m^2$) 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 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.

**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 to 47-fold, based on $IC_{50}$ 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 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 sensitised 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 anesthetised 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 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
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.

### 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
Waterford Road
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
Date of last renewal: 25th July 2021

## 10 DATE OF REVISION OF THE TEXT

January 2023