Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Domperidone 1mg/ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1mg of domperidone.

Excipients with known effect
Contains liquid sorbitol (non-crystallising, 400mg/ml), methyl parahydroxybenzoate (1.80mg/ml) and propyl parahydroxybenzoate (0.20mg/ml) (see section 4.4).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.

White to off-white, opaque, homogenous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Domperidone Suspension is indicated in adults for the relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

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

It is recommended to take Domperidone Oral Suspension 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 35 kg or more).

10 ml (of 1mg/ml oral suspension) up to three times per day with a maximum dose of 30ml per day.

Hepatic Impairment
Domperidone Oral Suspension 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 Oral Suspension should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see sections 4.4 and 5.2).

Paediatric population
The efficacy of domperidone in adolescents 12 years of age and weighing less than 35 kg has not been established.

4.3 Contraindications

Domperidone suspension is contraindicated in the following situations:
- Known hypersensitivity to domperidone or 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 drugs, with the exeption 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

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 30mg, and patients concurrently taking QT prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older.

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 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.

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.

Use with Potent CYP3A4 Inhibitors:
Co-administration with oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors that prolong the QTc interval should be avoided (see section 4.5).

Co-administration of levodopa:
Although no dosage adjustment of levodopa is deemed necessary, an increase of plasma levodopa concentration (max 30-40%) has been observed when domperidone was taken concomitantly with levodopa. See section 4.5.

Domperidone suspension contains 400mg ofliquid sorbitol (non-crystallising, E420) per ml, which may causegastrointestinal discomfort and a mild laxative effect. Patients with rare hereditary problems offructose intolerance (HFI) should not take this medicinal product.

This medicine contains less than 1 mmol sodium(23 mg) per 5ml, that is to say essentially 'sodium-free'.

Domperidone suspension contains methylhydroxybenzoate (E218) and propyl hydroxybenzoate (E216), which may causeallergic reactions (possibly delayed).

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 as they lower the oral bioavailability of domperidone.

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

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

Concomitant use of the following substances is contraindicated:
QTc-prolonging medicinal products
- 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, setindole)
- certain antidepressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g., erythromycin, lefloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antmalarial 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.

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 interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

Levodopa: Increase of plasma levels of levodopa (max 30-40%). See section 4.4

The above list of substances is representative and not exhaustive.

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.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies.

In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) and erythromycin monotherapy (500mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses (see section 5.3). 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 thechild and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

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 effects

Tabulated list of adverse reactions
The safety of domperidone was evaluated in clinical trials and in postmarketing 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 (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 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 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	Convulsion Extrapyramidal disorder
Eye disorders			Oculogyric crisis
Cardiac disorders (see section 4.4)			Ventricular arrhythmias QTc prolongation Torsades 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

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.

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

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. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.

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

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 A03

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 oesophaegeal 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 3.4msec 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 properties

Absorption
Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The Cmax and AUC values of domperidone increased proportionately 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.

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. 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.

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.

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 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 should not be used 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.

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 (10mg 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 (10mg 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 Torsades 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 anaesthetised guinea pig model following slow intravenous infurions, 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 admimistered 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

Liquid sorbitol (non crystallising, E420)
Microcrystalline cellulose (E460) and carmellose sodium
Saccharin sodium (E954)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Polysorbate 20 (E432)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.
In-use shelf life: 3 months

6.4 Special precautions for storage

Do not store above 25°C. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

A 200ml conventional amber soda glass (Type III) bottle fitted with a 28mm child resistant tamper evident cap. It is supplied with a 5ml dosing syringe and bottle adapter and packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

How to use the oral syringe

1. Shake the bottle well making sure the cap is firmly on the bottle.
2. Remove the cap. Note: keep the cap nearby to close the bottle after each use.
3. Push the plastic adapter into the neck of the bottle. Note: the adapter must always stay in the bottle.
4. Take the syringe and check the plunger is fully down.
5. Keep the bottle upright and insert the oral syringe firmly into the plastic adapter.
6. Turn the whole bottle with the syringe upside down.
7. Slowly pull the plunger down fully so that the syringe fills with medicine. Push the plunger back up completely to expel any large air bubbles that may be trapped inside the oral syringe.
8. Then pull the plunger slowly back to the volume you need for your dose.
9. Turn the whole bottle with the syringe the right way up and take the syringe out of the bottle.

10. The dose of medicine can now be swallowed directly from the oral syringe. Please ensure that you are sitting upright and the plunger must be pushed slowly to allow you to swallow the dose.
11. Replace the child resistant cap after use, leaving the adapter in place.
12. To clean the oral syringe, take apart by removing the plunger completely. Pull straight out of the barrel. The barrel and plunger can be washed with soap and water, rinsed, and allowed to dry. Do not wash the oral syringe in the dishwasher.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/050/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th December 2014
Date of last renewal: 5th November 2019

10 DATE OF REVISION OF THE TEXT

February 2020