Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Motilium 10mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains domperidone 10mg.

Excipients with known effect: Each film-coated tablet contains 54.2mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to faintly cream-coloured, circular biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

It is recommended to take Motilium 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.

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

Use in children under 12 years of age (and adolescents weighing less than 35kg):
Not recommended.

Patients > 60 years of age:
Patients older than 60 years of age should consult a healthcare professional before taking Motilium.

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

Renal Impairment
Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of Motilium Tablets 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).

4.3 Contraindications

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful: gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see section 5.2)
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see section 4.4)
- Co-administration with all 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)
- confirmed or suspected pheochromocytoma due to the risk of severe hypertension episodes.

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 4.5 and 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.

Patients older than 60 years should consult a healthcare professional before taking Motilium.

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

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

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

These tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosaemia or glucose/galactose malabsorption.

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 Motilium.

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.

Concomitant administration of anticholinergic drugs may antagonise the anti- dyspeptic effect of Motilium.
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)
- 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 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, saquinaver, 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 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited post marketing data on the use of domperidone in pregnant women. Therefore, Motilium Tablets 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 Motilium affects them.

4.8 Undesirable effects

The safety of Motilium 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 Motilium (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 (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), and 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		Dizziness Somnolence Headache Extrapyramidal disorder	Convulsion Restless leg syndrome*
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias QTc prolongation Torsade de Pointes Sudden cardiac death (see section 4.4 and 4.5)
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 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.

In postmarketing experience, there were no differences in the safety profile of adults and children with the exception of extrapyramidal disorder which occurred primarily in neonates and infants (up to one year of age) and other central nervous system-related effects of convulsion and agitation which were primarily reported in infants and children.

An increase in the risk of serious ventricular arrhythmias and sudden cardiac death have been reported in some epidemiology studies (see section 4.4).

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, Website: www.hpra.ie.

4.9 Overdose

Symptoms and signs.
Overdose has been reported primarily in infants and children.
Symptoms of overdosage may include agitation, altered consciousness, convulsion, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives
ATC Code: A03F A 03

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema.

Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 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 properties

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations, occurring at approximately 1 hour after dosing. The Cmax 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 The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when domperidone is taken after a meal.

Distribution

Oral Domperidone does not appear to accumulate or to 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.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

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

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

Renal impairment
In subjects with severe renal insufficiency (creatinine clearance<30 ml/min/1.73m2) 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-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* proarrhythmic 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 rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the 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 (10mg administered 3 times a day).

The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate
maize starch
microcrystalline cellulose
pregelatinised potato starch
povidone
magnesium stearate
hydrogenated vegetable oil
sodium laurilsulfate
hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister packs of aluminium foil/PVC containing 10 or 20 tablets, packed in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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