NAME OF THE MEDICINAL PRODUCT
MOTILIUM® (domperidone base)

QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 10 mg domperidone.
The oral suspension contains 1 mg domperidone per ml.
One suppository contains either 10 mg, 30 mg or 60 mg domperidone
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Film coated tablets.
Oral suspension.
Suppositories.

CLINICAL PARTICULARS
Therapeutic Indications
1. The dyspeptic symptom complex that is often associated with delayed gastric emptying, gastro-oesophageal reflux and oesophagitis:
- epigastric sense of fullness, early satiety, feeling of abdominal distension, upper abdominal pain;
- bloating, eructation, flatulence;
- nausea and vomiting;
- heartburn with or without regurgitations of gastric contents in the mouth.
2. Nausea and vomiting of functional, organic, infectious or dietary origin or induced by radiotherapy or drug therapy. A specific indication is nausea and vomiting induced by dopamine agonists, as used in Parkinson's disease (such as L-dopa and bromocriptine).
Posology and Method of Administration
It is recommended to take oral MOTILIUM before meals. If taken after meals, absorption of the drug is somewhat delayed.
Use in renal insufficiency
Since the elimination half life of domperidone is prolonged in severe renal impairment, on repeated administration the dosing frequency of MOTILIUM should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients on prolonged therapy should be reviewed regularly (see Pharmacokinetic Properties).
When MOTILIUM is used on prescription, the following dosing information applies:
Adults and adolescents ≥12 years of age and weighing ≥ 35 kg and children weighing ≥ 35 kg
The dose of MOTILIUM should be the lowest effective dose for the individual situation and can be increased if necessary to a maximum daily oral dose of 80 mg (or 120 mg for suppositories). The initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Film-coated tablets (10 mg/tablet)	1 to 2 tablets three to four times per day	80 mg (8 tablets)
Oral suspension (1 mg/ml)	10 ml to 20 ml three to four times per day	80 mg (80 ml of 1 mg/ml oral suspension
Suppositories (60 mg/suppository)	One 60-mg suppository two times per day	120 mg (2 X 60 mg suppositories)

Infants and children < 12 years of age and weighing < 35 kg, and adults and adolescents weighing < 35 kg
The dose of MOTILIUM should be the lowest effective dose. The total daily dose is dependent on weight (see table below). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children (see Undesirable Effects). Overdosing may cause nervous system disorders in children. The dose should be determined accurately and not exceed the recommended maximum individual and daily dose in neonates, infants, toddlers and small children. The initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed. Film-coated tablets are unsuitable for use in children, adults and adolescents weighing less than 35 kg. Suppositories are unsuitable for use in children weighing less than 5 kg.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Oral suspension (1 mg/ml)	0.25 – 0.5 mg/kg three to four times per day	80 mg (2.4 mg/kg but no more than 80 ml)
Suppositories 10 mg /suppository 30 mg /suppository	For a child weighing 5-15 kg: One 10-mg suppository two times per day. For a child weighing more than 15 kg: One 30-mg suppository two times per day.	20 mg (2x10mg suppository) 60 mg (2x30mg suppository)

When MOTILIUM is not prescribed by a doctor and is used Over the Counter, the following dosing information applies:

Adults and adolescents ≥ 12 years of age and weighing ≥ 35 kg

If MOTILIUM is not used under medical supervision:

- MOTILIUM can be taken to a maximum daily dose of 40 mg.
- Therapy with MOTILIUM should not exceed 14 days of continuous treatment without medical consultation.

Infants and children under 12 years old

NOTE: Tablets are unsuitable for use in children weighing less than 35 kg.

Contraindications

MOTILIUM is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- Co-administration with oral ketoconazole, erythromycin, or other potent CYP3A4 inhibitors which prolong the QTc interval such as fluconazole, voriconazole, clarithromycin, amiodarone, and telithromycin (see Interaction with other medicinal products and other forms of interaction).
- Whenever stimulation of gastric motility might be dangerous, e.g. in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation
- In patients with moderate or severe hepatic impairment (See Pharmacokinetic Properties)

Special Warnings and Special Precautions for Use

MOTILIUM should be used with caution in older patients or those with current or a history of cardiac disease. Some epidemiological studies have shown domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Undesirable Effects). Those studies suggest this increased risk may be higher in patients older than 60 years of age or in patients taking oral doses greater than 30 mg per day.

Antacids or antisecretory agents should not be taken simultaneously with oral formulations of MOTILIUM, as they lower the oral bioavailability of domperidone (see Interactions with Other Medicinal Products and Other Forms of Interaction). When used concomitantly, MOTILIUM should be taken before meals and antacids or antisecretory agents after meals.

The film-coated tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosemia or glucose/galactose malabsorption.

The oral suspension contains sorbitol and may be unsuitable for patients with sorbitol intolerance.

Interactions with Other Medicinal Products and Other Forms of Interaction

Antacids or antisecretory agents should not be given simultaneously with oral formulations of MOTILIUM as they lower the oral bioavailability of domperidone (see also Special warnings and special precautions for use).

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

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* and human data show that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Examples of potent CYP3A4 inhibitors include:

- Azole antifungals, such as flucoanazole*, itraconazole, ketoconazole*, and voriconazole*;
- Macrolide antibiotics, such as clarithromycin* and erythromycin*:
- HIV protease inhibitors, such as amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, and saquinavir:
- Calcium antagonists, such as diltiazem and verapamil:

- Amiodarone*
- Aprepitant
- Nefazodone
- Telithromycin*

(*also prolong the QTc interval; see Contraindications)

Separate 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 domperidone 10 mg four times daily and ketoconazole 200 mg 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 erythromycin 500 mg 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. (See Contraindications)

The contribution of increased plasma concentrations of domperidone to the observed effect on QTc is not known.

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

In another multiple-dose study in healthy subjects, no significant increases in QTc were noted during steady state treatment with domperidone monotherapy at 40 mg four times daily (total daily dose of 160 mg, which is double the maximum daily dose) at plasma concentrations of domperidone that were at least similar to those found in the combination arms of the interaction studies.

Theoretically, since MOTILIUM has gastro-kinetic effects it could influence the absorption of concomitantly orally administered drugs, particularly those with sustained release or enteric coated formulations. However, in patients already stabilised on digoxin or paracetamol, concomitant administration of domperidone did not influence the blood levels of these drugs.

MOTILIUM may also be given with:

- neuroleptics, the action of which it does not potentiate,
- dopaminergic agonists (bromocriptine, L-dopa), whose unwanted peripheral effects such as digestive disorders, nausea and vomiting it suppresses without counteracting their central properties.

Pregnancy and Lactation

Use during 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, MOTILIUM should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Use during lactation

The drug is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800 ng/ml after oral and i.v. administration of 2.5 mg/kg respectively). Domperidone concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations and expected not to exceed 10 ng/ml. The total amount of domperidone excreted in human breast milk is expected to be less than 7 μg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore, breast-feeding is not recommended for mothers who are taking MOTILIUM.

Effects on Ability to Drive and Use Machines

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

Undesirable Effects

Clinical trial data

The safety of MOTILIUM was evaluated in 1221 patients with gastroparesis, dyspepsia, gastro-oesophagoeal reflux disorder (GERD), or other related conditions in 45 clinical trials included in the safety database. All patients were ≥ 15 years old and received at least one dose of oral MOTILIUM (domperidone base). Slightly fewer than one-half (553/1221) of patients were diabetic. The median total daily dose was 80 mg (range 10 to 160 mg), with 230 patients receiving a dose greater than 80 mg. Median duration of exposure was 56 days (range 1 to 2248 days).

Adverse drug reactions (ADRs) reported by ≥1% of patients treated with MOTILIUM in these 45 clinical trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥ 1% of MOTILIUM-Treated Patients in 45 Clinical Trials

System/Organ Class Adverse Reaction	**MOTILIUM (n=1221) %**
Psychiatric Disorders	
Depression	2.5
Anxiety	1.6
Libido Decreased/Loss of Libido	1.5
Nervous System Disorders	
Headache	5.6
Somnolence	2.5
Akathisia	1.0
Gastrointestinal Disorders	
Diarrhoea	5.2
Skin and Subcutaneous Tissue Disorders	
Rash	2.8
Pruritus	1.7
Reproductive System and Breast Disorders	
Breast Enlargement/Gynaecomastia	5.3
Breast Tenderness	4.4
Galactorrhoea	3.3
Amenorrhoea	2.9
Breast Pain	2.3
Menstruation Irregular	2.0
Lactation Disorder	1.6
General Disorders and Administration Site Conditions	
Asthenia	1.9

ADRs that occurred in <1% of MOTILIUM-treated patients in the 45 clinical trials (n=1221) are listed below in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% MOTILIUM-Treated Patients in 45 Clinical Trials

System/Organ Class Adverse Reaction	**MOTILIUM (n=1221) %**
Immune System Disorders	
Hypersensitivity	0.2
Skin and Subcutaneous Tissue Disorders	
Urticaria	0.7
Reproductive System and Breast Disorders	
Breast Discharge	0.8
Breast Swelling	0.5

The following adverse reaction has been reported with over-the-counter use: dry mouth.

Postmarketing

In addition to the ADRs reported during clinical studies and listed above, the following ADRshave been reported during postmarketing experience (Table 3). In each table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥ 1/ 1000 and < 1/100
Rare	≥1/10000 and < 1/1000
Very rare	<1/10000, including isolated reports.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with MOTILIUM by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very rare	Anaphylactic Reaction (including Anaphylactic Shock)
Psychiatric Disorders	
Very rare	Agitation^, Nervousness
Nervous System Disorders	
Very rare	Extrapyramidal Disorder^, Convulsion^
Cardiac Disorders	
Very rare	Sudden Cardiac Death*, Serious Ventricular Arrhythmias* (see Special Warnings and Special Precautions for Use)
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema
Renal and Urinary Disorders	
Very rare	Urinary Retention
Investigations	
Very rare	Liver Function Test Abnormal, Blood Prolactin Increased

*Based on epidemiology data

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

Overdose

Symptoms

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

Treatment

There is no specific antidote to domperidone, 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 is recommended. Anticholinergic or anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Propulsives, ATC Code: A03FA03

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 oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Pharmacokinetic Properties

Absorption

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations at 30 to 60 minutes. 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 base. Oral bioavailability of domperidone base 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 the oral drug is taken after a meal.

The bioavailability of a 60 mg suppository after single or repeated dosing is approximately 65% of 80 mg of oral tablets given over 24 hours. After rectal administration of 60-mg suppositories, mean domperidone plasma concentrations between 20 and 40 ng/ml are maintained from approximately 0.5 to 5 hours after single- and multiple-dose administration. Following single-dose administration, mean peak plasma levels of 60 mg suppositories are 89% of that of two 10 mg oral tablets, but the mean dose-normalized rectal bioavailability relative to oral tablets is 64%. Following multiple-dose administration, mean peak plasma levels and dose normalized bioavailability of 60 mg suppositories administered every 12 hours are 63% and 66%, respectively, of two 10 mg oral tablets administered every 6 hours.

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.

Special Populations

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. (See Contraindications.)

Renal impairment

In subjects with severe renal insufficiency (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L) the half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in subjects with normal renal function. Very little unchanged drug (approximately 1%) is excreted via the kidneys. (See Posology and Method of Administration.)

Pediatric patients

Based on limited pharmacokinetic data, domperidone plasma concentrations in preterm neonates were consistent with those reported in adults..

Preclinical Safety Data

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.

Electrophysiological *in vitro* and *in vivo* studies have shown that domperidone, at high concentrations, may prolong the QTc interval.

PHARMACEUTICAL PARTICULARS

List of Excipients

Film coated tablets

Lactose, maize starch, microcrystalline cellulose, pregelatinized potato starch, polyvidone, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulphate, hypromellose.

Oral suspension

Sodium saccharin, microcrystalline cellulose and sodiumcarboxymethylcellulose, sorbitol liquid non-crystallising, methylparahydroxybenzoate, propylparahydroxybenzoate, sodium hydroxide, polysorbate, purified water.

Suppositories

Polyethylene glycol, tartaric acid, butylated hydroxyanisole.

Incompatibilities

None known.

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Keep out of reach of children.

Tablets, Oral suspension

No special storage conditions required.

Suppositories

Do not store above 25°C.

Nature and Contents of Container

Blister packs with 10 mg tablets.

Oral suspension in 100 ml or 200 ml glass bottles with a 10 ml dosing cup or a 5 ml dosing pipette.

Blister packs with 10 mg, 30 mg or 60 mg suppositories.

Instructions for Use and Handling

Oral Suspension

Mix the contents of the bottle completely using a gentle tilting motion to avoid the formation of foam.

Directions for opening the bottle:

Fig. 1: The bottle comes with a childproof cap, and should be opened as follows:

- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

Directions for using the pipette (supplied with 100 ml bottle only):

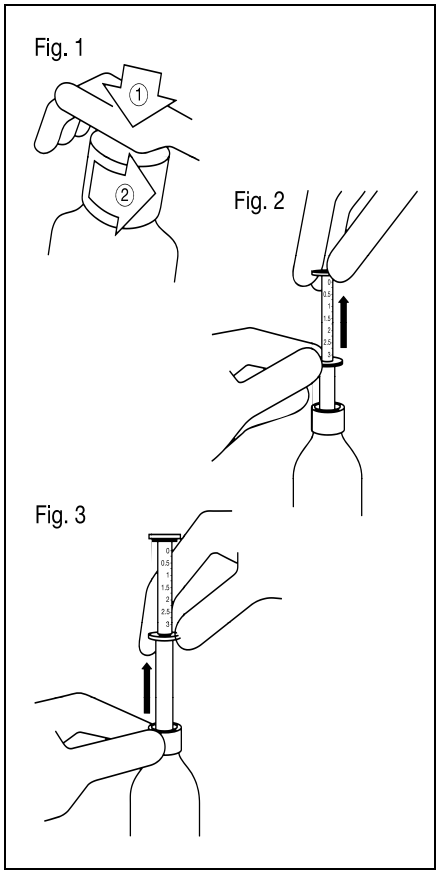
Fig. 2: Insert the pipette into the bottle. While holding the bottom ring, pull the top ring up to the mark corresponding to the child’s weight in kilograms.

Fig. 3: Holding the bottom ring, remove the entire pipette from the bottle.

Empty the pipette.

Close the bottle.

Rinse the pipette with some water.



MANUFACTURED BY
See outer carton.

DATE OF REVISION OF THE TEXT
July 2012