Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Motilium 60 mg Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One suppository contains domperidone 60mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suppositories
White to slightly yellow suppositories.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
The relief of the symptoms of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.

Children
The relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

The initial duration of treatment is four weeks. Patients should be re-evaluated after four weeks and the need for continued treatment re-assessed. Therapy should not exceed 14 days of continuous treatment without medical consultation.

See section 4.4 for further information.

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

60 mg suppositories two times per day with a maximum daily dose of 120 mg.

Infants and children under 12 years of age and weighing less than 35kg

The total daily dose is dependent on the child's weight:

– 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

Suppositories are unsuitable for use in children weighing less than 5 kg.

Hepatic Impairment

Motilium 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 Motilium 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)

4.3 Contraindications

Motilium is contraindicated in the following situations:

– known hypersensitivity to domperidone or any of the excipients

– prolactin-releasing pituitary tumour (prolactinoma).

Motilium should not be used

• 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).

4.4 Special warnings and precautions for use

Precautions for use

The suppositories contain butylated hydroxyanisole which can irritate eyes, skin and the lining of the mouth and nose (mucous membranes).

Use during lactation

The total amount of domperidone excreted in human breast milk is expected to be less than 7µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore Motilium is not recommended in breast-feeding women.

Use in infants

Although neurological side effects are rare (see "Undesirable effects" section), the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life.

Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration of Motilium, 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. Such patients on prolonged therapy should be reviewed regularly (see section 5.2).

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).

Cardiovascular effects:

Some epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). The risk may be higher in patients older than 60 years or with daily doses more than 30 mg. Domperidone should be used at the lowest effective dose in adults and children.

Use of domperidone and other drugs which prolong QTc intervals requires that caution be exercised in patients who have existing prolongation of cardiac conduction intervals, particularly QTc, and patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.

4.5 Interaction with other medicinal products and other forms of interaction

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 CYP3 A4 mediated first pass metabolism by these drugs.

With the combination of oral 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 10 mg four times daily and oral 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. In these studies domperidone monotherapy at 10 mg 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 (200 mg twice daily) and erythromycin monotherapy (500 mg 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

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.

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 micrograms per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore, Motilium is not recommended in breast-feeding women.

4.7 Effects on ability to drive and use machines

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

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 can not be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	Adverse Drug Reaction Frequency	
	Common	Uncommon
Psychiatric disorders		Loss of libido Anxiety
Nervous system disorders		Somnolence Headache
Gastrointestinal disorders	Dry mouth	Diarrhoea
Skin and subcutaneous tissue disorder		Rash Pruritus
Reproductive system and breast disorders		Galactorrhoea Breast pain Breast tenderness
General disorders and administration site conditions		Asthenia

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.

Postmarketing experience

In addition to the adverse effects reported during clinical studies and listed above, the following adverse drug reactions have been reported.

Immune system disorders
Not known Anaphylactic reaction (including anaphylactic shock)

Psychiatric disorders
Not known Agitation, nervousness

Nervous system disorders
Not known Convulsion, extrapyramidal disorder

Eye disorders
Not known Oculogyric crisis

Cardiac disorders (see section 4.4)
Not Known Ventricular arrhythmias, sudden cardiac death, QTc prolongation

Skin and subcutaneous tissue disorders
Not known Urticaria, angioedema

Renal and urinary disorders
Not known Urinary retention

Reproductive system and breast disorders
Not known Gynaecomastia, amenorrhoea

Investigations
Not known Liver function test abnormal, blood prolactin increased

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Extrapyramidal disorder occurs primarily in neonates and infants.

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

4.9 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 overdose, gastric lavage, as well as the administration of activated charcoal, may be useful. Close medical supervision and supportive therapy is 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 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.

5.2 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. 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 the oral drug is taken after a meal.

The bioavailability of a 60mg suppository after single or repeated dosing is approximately 65% of 80mg of oral tablets, given over 24 hours. After rectal administration of 60 mg domperidone suppositoriesmean 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 88% 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, 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 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 (see section 4.3)

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.

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 section 4.4).

Paediatric population

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In *in vitro* experiments on isolated cells transfected with HERG and on isolated guinea pig myocytes, exposure ratios ranged between 5- and 30-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 20 mg (q.i.d.). Exposure 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 (20mg q.i.d.) by 17-fold. However, safety margins in *in vitro* pro-arrhythmic models (isolated Langendorff perfused heart) and in *in vivo* models (dog, guinea pig, rabbits sensitised for torsades de points) exceeded the free plasma concentrations in humans at maximum daily dose (20mg q.i.d.) by more than 17-fold. In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 10- 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

Macrogol 4000
Macrogol 1000
Macrogol 400
Tartaric acid
Butylated hydroxyanisole

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Keep container in the outer carton to protect from light.

6.5 Nature and contents of container

Alu/PE foil blister strips consisting of printing primer, aluminium (45 micrometre) and polyethylene (inner layer) containing 6 suppositories, packed in a cardboard carton.

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

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0823/051/005

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