PRODUCT NAME
MOTILIUM Tablet 10mg
QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 10 mg domperidone.

PHARMACEUTICAL FORM
Film coated tablets.

CLINICAL PARTICULARS
Therapeutic Indications
Domperidone is indicated for the relief of the symptoms of nausea and vomiting.

Nausea and vomiting of functional, organic, infectious or dietary origin.

Nausea and vomiting induced by
- radiotherapy or drug therapy.
- dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease.

Dosage and Administration
It is recommended to take oral domperidone15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.

1. Adults and adolescents ≥ 12 years of age and weighing ≥35 kg and children <12 years of age and weighing ≥ 35 kg

The dose of domperidone should be the lowest effective dose for the individual situation (typically 30 mg/day) and can be increased if necessary to a maximum daily oral dose of 40 mg.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their physician. For other indications, 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 tablet three to four times per day	40 mg (4×10 mg tablet).

2. Adults and adolescents (≥ 12 years of age) weighing < 35 kg

The dose of domperidone should be the lowest effective dose. The total daily dose is dependent on body weight.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. For other indications, 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. Due to the need for accurate dosing, tablets are unsuitable for use in adults and adolescents weighing less than 35kg.

3. Infants and children < 12 years of age and weighing < 35 kg
   The efficacy of domperidone has not been established in infants and children < 12 yearsof age and weighing < 35 kg (see *Clinical Studies*).

Renal impairment
Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L), 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. Patients with severe renal impairment should be reviewed regularly (see *Pharmacokinetic Properties*).

Hepatic impairment
Domperidone is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment (see *Contraindications*). Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment (see *Pharmacokinetic Properties*).

Contraindications
Domperidone is contraindicated in the following situations:
- Hypersensitivity to domperidone or any of the ingredients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- 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 Warnings and Precautions).
- co-administration with QT-prolonging drugs (see Interactions)
- co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects) (see Interactions).
- 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).

Warnings and Precautions
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 Adverse Reactions).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Adverse Reactions). A higher riskwas 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. Therefore, domperidone should be used with caution in older patients.

Patients older than 60 years of age should consult their physician before taking domperidone.

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 Contraindications).

Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) and bradycardia areknown 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 patient should promptly consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Drug interaction potential
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. Co-administration of domperidone with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (see *Contraindications*).

Caution should be exercised when domperidone is co-administered with potent CYP3A4 inhibitors which have not been shown to cause QT interval prolongation such as indinavir and patients should be monitored closely for signs or symptoms of adverse reactions (see *Adverse Reactions*).

Caution should be exercised when domperidone is co-administered with drugs which have been shown to cause QT interval prolongation and patients should be monitored closely for signs or symptoms of cardiovascular adverse reactions (see *Adverse Reactions*). Examples include:

- anti-arrhythmics class IA (e.g., disopyramide, 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., levofloxacin, moxifloxacin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (e.g., halofantrine)
- certain gastro-intestinal drugs (e.g., dolasetron)
- certain drugs used in cancer (e.g., toremifene, vandetanib)
- certain other drugs (e.g., bepridil, methadone)

Antacids or antisecretory agents should not be taken simultaneously with oral formulations of domperidone, as they lower the oral bioavailability of domperidone. When used concomitantly, domperidone should be taken before meals and antacids or antisecretory agents after meals.

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

Interactions
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.

When domperidone was co-administered with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation, clinically relevant changes in QT intervals were observed. Therefore, co-administration of domperidone with certain drugs is contraindicated (see Contraindications).

Concomitant administration of anticholinergic drugs (e.g., dextromethorphan, diphenhydramine) may antagonize the anti-dyspeptic effect of domperidone.

Theoretically, since domperidone 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.

Domperidone 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
Pregnancy
There are no adequate and well-controlled studies in pregnant or breastfeeding women. This product should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus or breastfeeding infant. Ask a physician before use if you are pregnant or breastfeeding.

Lactation
The amount of domperidone that could be ingested by an infant through breast milk is low. The maximal relative infant dose (%) is estimated to be about 0.1% of the maternal weight- adjusted dosage. It is not known whether this is harmful to the newborn. Therefore, breast- feeding is not recommended for mothers who are taking domperidone.

Effects on Ability to Drive and Use Machines
Dizziness and somnolence have been observed following use of domperidone (see Adverse Reactions). Use caution when driving a motor vehicle or operating machinery.

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of domperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with domperidone cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates

observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The safety of domperidone was evaluated in 1221 patients with gastroparesis, dyspepsia, gastro-oesophageal reflux disorder (GERD), or other related conditions in 45 clinical trials included in the safety database. All patients were at least15 years old and received at least one dose of oral 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).

ARs reported by ≥1% of patients treated with domperidone in these 45 clinical trials are shown in Table 1.

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

System/Organ Class Adverse Reaction	**Domperidone (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

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

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

System/Organ Class Adverse Reaction	Domperidone (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

Adverse drug reactions (ADRs) identified during post marketing experience with domperidone are included in Table 3. The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/ 1,000 and < 1/100
Rare	≥1/10,000 and < 1/1,000
Very rare	<1/10,000, including isolated reports.
Not known	(cannot be estimated from the available data)

In Table 3, ADRs identified are presented by frequency category based 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.

Table 3. Adverse Reactions Identified During Postmarketing Experience with Domperidone 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	Dizziness, Extrapyramidal Disorder, Seizure
Cardiac Disorders	
Very rare	Ventricular arrhythmias (serious)*, QTc prolongation, Torsade de Pointes, Sudden cardiac death* (seeWarnings and Precautions)
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

Pediatric population
In postmarketing experience, there were no differences in the safety profile of adults and children.

Overdose
Symptoms and signs
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. Close medical supervision and supportive therapy is recommended.
Keep out of reach of children. In the event of overdose, get medical help or contact a Poison Control Center right away.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties

Pharmacotherapeutic group: Propulsive, 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 esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Effect on QT/QTc Interval and Cardiac Electrophysiology

In accordance with ICH—E14 guidelines, a thorough QT study was performed in healthy subjects. This study included a placebo, active comparator and positive control and was conducted using recommended and supra-therapeutic doses (10 and 20 mg administered 4 times a day). 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, and the 2-sided 90% CI (1.0 - 5.9 msec) did not exceed 10 msec. In another study involving Chinese healthy adult subjects, a randomized, placebo- and positive controlled, multiple-dose, single-center, Phase 1, 4-way crossover design, was utilized to assess the effects of domperidone (10 and 20 mg thrice daily) on the QTc interval duration. In this study, the largest difference in LS mean from placebo of change from baseline was 2.7 msec for 20 mg tid on Day 4, and the 2-sided 90% CI (0.46 – 4.99 msec) also did not exceed the 10 msec threshold in the ICH-E14. The QTprolongation observed in both of these studies, when domperidone was administered according to the recommended dosing regimen were not clinically relevant.

This lack of clinical relevance is corroborated by pharmacokinetics and QTc interval data from two older studies which involved a 5-day treatment of 20 mg and 40 mg domperidone administered 4 times a day. ECGs were recorded prior to the study, on Day 5 at 1 hour (approximately at t_{max}) after the morning dose, and 3 days later. In both studies, no difference between QTc after active treatment and placebo was observed. It was therefore concluded that domperidone administration of 80 and 160 mg daily doses had no clinically significant effect on QTc in healthy subjects.

Clinical Studies

Infants and children ≤ 12 years of age

A multicenter, double-blind, randomized, 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), randomized 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 the percentage of subjects with no vomiting episodes during the first 48 hours after the first treatment administration.

Pharmacokinetic Properties

Absorption

A significant difference was observed in the absorption of domperidone between fasting and fed subjects. Following oral administration of 10 mg domperidone tablet, the mean Tmax

values in fasting and fed subjects was 0.79 hours and 1.66 hours, respectively. The mean peak concentration values in fasting and fed subjects are 16.97 μg/L and 15.11 μg/L, respectively. The mean AUC0–t values in fasting and fed subjects are 56.76 h×μg/L and 75.71 h×μg/L, respectively. The mean AUC0–∞ values in fasting and fed subjects are 64.58 h×μg/L and 86.48 h×μg/L, respectively.

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. The mean volume of distribution for the terminal disposition phase (Vz/F) values of domperidone in fasting and fed subjects are 1.92 L and 1.53 L, respectively. The mean oral dose clearance (Cl/F) values in fasting and fed subjects are 0.20 L/h and 0.12 L/h, respectively.

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. The terminal-phase elimination half-life (T1/2) of domperidone in fed subjects is 8.72 hours, while in fasting subjects it is only 7.15 hours.

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. (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 Dosage and Administration.)

Pre-Clinical Safety Data

General toxicology

Domperidone has moderate acute toxicity in animals. In chronic oral studies no toxic effects except for prolactin related effects, were observed at 10 and 2.5 mg/kg in rats and dogs, respectively. Preclinical evidences indicate a safety fold of 36-71x for the QT prolongation with respect to maximum recommended therapeutic dose.

Genetic toxicology

Domperidone is not mutagenic or clastogenic in in vitro and in vivo genotoxicity assays.

Carcinogenicity

Domperidone was administered to mice for 18 months and rats for 24 months in carcinogenicity studies. No dose-related effects were observed except for an increased incidence of malignant mammary (mice, rat) and pituitary (male rat) tumors at 25 times the maximum human dose.

Teratogenicity

At a high, maternally toxic dose of 200 mg/kg/day (40 times of maximum human dose), teratogenic effects were seen in the rats. The clinical significance of these findings is unknown. No teratogenicity was observed in mice and rabbits.

Fertility

Domperidone did not impact fertility up to the dose 160 mg/kg/day in male and female rats.

PHARMACEUTICAL PARTICULARS

List of Excipients

Domperidone base

Film Coated Tablets

Lactose monohydrate, maize starch, microcrystalline cellulose, pregelatinized potato starch, polyvidone K-90, magnesium stearate, hydrogenated vegetable oil, sodium lauryl sulphate, purified water.

Incompatibilities

None Known.

Shelf-life

See expiry date on the outer pack.

Special Precautions for Storage

Store below 30°C.

Keep out of sight and reach of children.

Nature and Contents of Container

Blister packs with 25 x 10 mg tablets. One box contains 100 tablets.

MANUFACTURER
Film Coated Tablets
JNTL Consumer Health (France) SAS
Domaine De Maigremont,
27100 Val De Reuil, France.

PRODUCT REGISTRATION HOLDER
JNTL (Malaysia) Sdn. Bhd.
Lot 3 & 5 Jalan Tandang,
46050 Petaling Jaya, Selangor,
Malaysia.

DATE OF REVISION OF THE TEXT
7 January 2025 (Based on CCDS vJan2024)