1 NAME OF THE MEDICINE
Domperidone maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains domperidone maleate, as the active ingredient.

Each tablet contains 10 mg domperidone (as maleate), as the active ingredient.

Excipients with known effect
Lactose monohydrate

For the full list of excipients see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM
White round, biconvex uncoated tablet with the inscription ‘Dm 10’ on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Domperidone is indicated for the short-term treatment in adults of:

• Symptoms associated with idiopathic or diabetic gastroparesis (once control of diabetes has been established by diet and/or insulin, an attempt should be made to discontinue domperidone).

• Intractable nausea and vomiting from any cause.

4.2 DOSE AND METHOD OF ADMINISTRATION
APO-Domperidone tablets are intended for oral administration.

Dosage

Long-term use and use with medicines that prolong the QT interval or medicines that inhibit CYP3A should be avoided. The lowest dose needed to alleviate symptoms should be taken for the shortest period of time (see section 4.4 Special warnings and precautions for use - Cardiac effects).

Domperidone should be taken 15-30 minutes before meals and, if necessary, before retiring. 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.

Adults - 10 mg three times daily. Domperidone should be initiated at the lowest effective dose for the individual situation, which may be adjusted upward with caution to achieve the desired effect. The expected benefit of an increased dose should outweigh the potential risks. 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 limited to 4
weeks. Patients should undergo a benefit/risk re-analysis if treatment beyond 4 weeks is contemplated.

The maximum daily dose is 30 mg.

Safety and efficacy of domperidone use beyond six months has not been established.

Renal impairment

**In patients with severe renal insufficiency** - (creatinine serum > 0.6 mmol/L) 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 is excreted via the kidneys, it is unlikely that the dose needs to be adjusted for single acute administration in patients with renal insufficiency. However, on repeated administration, the dosing frequency will need to 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 on prolonged therapy should be reviewed regularly (see section **5.2 Pharmacokinetic properties**).

**Food** - It is recommended that domperidone be taken 15-30 minutes 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.

Hepatic impairment

Domperidone is contraindicated for patients with moderate or severe hepatic impairment (see section **4.3 Contraindications**).

### 4.3 CONTRAINDICATIONS

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- Co-administration with potent CYP3A4 inhibitors (see sections **4.4 Special warnings and precautions for use** and **4.5 Interactions with other medicines and other forms of 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 section **5.2 Pharmacokinetic properties**).
- 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.
- Co-administration with medicines that prolong the QTc interval (see sections **4.4 Special warnings and precautions for use** and **4.5 Interactions with other medicines and other forms of interactions**).

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Antacids or antisecretory drugs should not be taken simultaneously with domperidone since they reduce its oral bioavailability of domperidone (see section **4.5 Interactions with other medicines and other forms of interactions**). When used concomitantly, Domperidone should be taken before meals and antacids or antisecretory agents after meals.
Cardiac effects

Domperidone is associated with an increased risk of sudden cardiac death of approximately 4 per 1000 per years compared with no use of medication. This risk is increased in patients aged over 60 years or who have cardiac disease or diabetes. The risk is also increased with domperidone doses > 30 mg daily and when taken in combination with medicines that prolong the QT interval and medicines that inhibit CYP3A4.

 Concurrent use of domperidone with medicines that prolong the QTc interval is contraindicated.
 Concurrent use of domperidone with medicines that are potent inhibitors of CYP3A4 is contraindicated. (see sections 4.3 Contraindications and 4.5 Interactions with other medicines and other forms of interactions).

 Concurrent use of domperidone with medicines that are moderate inhibitors of CYP3A4 should be avoided. Long term use of domperidone should be avoided. The lowest dose needed to alleviate symptoms should be taken for the shortest period of time.

Domperidone should be used with caution in older patients or those with current or a history of cardiac disease.

In a case-control study by van Noord et al (2010), the odds of sudden cardiac death with current domperidone use (10 cases) were two-fold higher than the odds of sudden cardiac death in matched controls from the general population (adjusted odds ratio, 1.99 [95% CI: 0.80 - 4.96]). The adjusted odds ratio for sudden cardiac death in current users of a dose higher than 30 mg daily, relative to matched controls from the general population, was 11.4 (95% CI: 1.99 - 65.2) based on 4 identified cases. In a larger case-control study by Johannes et al (2010), the adjusted odds ratio for the composite of sudden cardiac death and serious ventricular arrhythmias was 1.44 (95% CI: 1.12 - 1.86) for current domperidone users relative to current proton-pump inhibitor users.

A population based, case-control study nested in a cohort of 681,104 patients with at least one recorded prescription for domperidone, any proton pump inhibitor medication, or metoclopramide found 90 cases of out-of- hospital Sudden Cardiac Death (SCD) with current domperidone use.

The incidence rate of SCD per 1,000 person-years with current usage of domperidone was 4.47 (95% CI: 43.59 – 5.49). This was higher than that for during person-time with no use of any of the study medications (0. 87; 95% CI: 0.82 – 0.92).

After adjusting for demographic characteristics, medical conditions, medications, and other potentially confounding factors, the point estimate for current use of domperidone compared with non-use of study medications was OR, 1.71(95% CI: 0.92 – 3.18).

In all of the medication group strata, the incidence increased with age, was higher in men than women, and was higher in those with diabetes than without.

With exposure to domperidone, the highest OR for SCD was with current exposure to only domperidone for 8-14 days (adjusted OR, 7.77; 95% CI: 1.70 – 35.53). The adjusted OR was 1.69 (95% CI: 0.38 - 7.57) for exposure of ≤ 7 days and 1.12 (95% CI: 0.50 – 2.53) for durations of ≥ 15 days. The risk of SCD compared with no exposure was highest for those prescribed > 30 mg/day (adjusted OR, 3.20; 95% CI: 0.59 – 17.34).

When domperidone was taken concomitantly with any QTc prolonging agent associated with torsade de pointes the risk of SCD increased from an adjusted OR of 1.64 (95% CI: 0.73 – 3.72) to 4.95 (95% CI: 0.84 – 29.07).
Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) and bradycardia are known 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.

**Prolactin levels**

There are limited safety data in long-term use (i.e. beyond six months) of domperidone. However, it has been shown to produce an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the drug (see section 4.8 Adverse effects (Undesirable effects)). (During oral administration of 30 mg daily for two weeks the plasma prolactin level measured 90 minutes after drug intake remained fairly constant at 25 ng/mL in males (normal value was 5 ng/mL) whilst in females the level of 117 ng/mL after the first dose decreased to 56 ng/mL after 14 doses (pretreatment normal value was 9 ng/mL).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of domperidone is contemplated in a patient with a past history of breast cancer.

Endocrine disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with drugs which stimulate prolactin release. The clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of domperidone and other prolactin stimulating drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis.

Domperidone does not affect plasma growth hormone or aldosterone.

Despite the lack of penetration of the blood-brain barrier, the possibility that extrapyramidal symptoms may occur in very rare instances after long-term use of domperidone, should be considered.

**Use in renal impairment**

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration 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. Such patients on prolonged therapy should be reviewed regularly (see sections 5.2 Pharmacokinetic properties and 4.2 Dose and method of administration).

**Use in the elderly**

No data available.

**Paediatric use**

Domperidone should not be used in children.

**Effects on laboratory tests**

No data available.
4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicines that prolong the QTc interval

Co-administration with medicines that prolong the QTc interval is contraindicated due to an increased risk of sudden cardiac death shown in post-market studies (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Examples of QTc-prolonging medicines include:

- Anti-arrhythmics class IA (e.g. disopyramide)
- Anti-arrhythmics class III (e.g. amiodarone*, dronedarone, sotalol)
- Some antipsychotics (e.g. haloperidol)
- Some antidepressants (e.g. citalopram, escitalopram)
- Some antibiotics (e.g. erythromycin*, clarithromycin*, levofloxacin, moxifloxacin)
- Some antifungal agents (e.g. pentamidine)
- Some antimalarial agents (e.g. lumefantrine)
- Some azole antifungals (e.g. itraconazole*, ketoconazole*, voriconazole*, fluconazole*)
- Some calcium antagonists (e.g. diltiazem*, verapamil*)
- Some gastrointestinal agents (e.g. prucalopride, granisetron, ondansetron)
- Certain HIV protease inhibitors (e.g. atazanavir*, fosamprenavir*, indinavir*, ritonavir*, saquinavir*)
- Some antineoplastic agents (e.g. toremifene, vandetanib)
- Others (e.g. aprepitant* and methadone)

*Also potent CYP3A4 inhibitors (see sections 4.3 Contraindications)

Potent CYP3A4 inhibitors

The main metabolic pathway of domperidone is through the cytochrome P450 isoenzyme 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.

Concurrent use of domperidone with medicines that are potent inhibitors of CYP3A4 is contraindicated due to an increased risk of sudden cardiac death shown in postmarket studies (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Examples of potent CYP3A4 inhibitors include:

- Azole antifungals, such as fluconazole^, 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^;
- Telithromycin^;
- Nefazodone

^Also prolong the QTc interval; (see section 4.3 Contraindications)
Separate pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed domperidone $C_{max}$ increases < 3 fold under maximal CYP3A4 inhibition by these drugs.

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. 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 10 mg 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 $C_{max}$ and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies (see section 4.3 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 of 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 4.8 msec, respectively, over the observation period.

**Moderate CYP3A4 inhibitors**

Concurrent use of domperidone with medicines that are moderate inhibitors of CYP3A4 should be avoided due to an increased risk of sudden cardiac death shown in post-market studies (see section 4.4 Special warnings and precautions for use).

**Miscellaneous interactions**

Antacids or antisecretory drugs should not be taken simultaneously with domperidone since they reduce its oral bioavailability (i.e., they should be taken after meals and not before meals) (see section 4.4 Special warnings and precautions for use). Dosing with these agents should be separated from dosing with domperidone by at least 2 hours.

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptic effects of domperidone. If administered prior to atropine, domperidone reduces the relaxant effect of atropine upon the lower oesophageal sphincter, but has no reversing effect if atropine is administered first.

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

Domperidone has been used with:

- dopaminergic agonists (bromocriptine, L-dopa) for suppression of unwanted peripheral effects such as digestive disorders, nausea and vomiting, without affecting their central activity.
4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category B2

Small amounts of domperidone have been found in rat foetal tissues. Reproduction studies were performed in rats with daily doses of domperidone up to 160 mg/kg orally and 40 mg/kg intravenously and in rabbits with daily doses up to 40 mg/kg orally and 1.25 mg/kg intravenously. There was no evidence of drug related dysmorphogenesis. There are however no adequate and well controlled studies in pregnant women. The potential risk for humans is unknown. Because animal studies are not always predictive of human response and there are limited post-marketing data on the use of domperidone in pregnant women, this drug should be used during pregnancy only if clearly needed.

Use in lactation

The amount of domperidone that could be ingested by an infant through breast milk is extremely 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 women who are taking domperidone.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness and somnolence have been observed following use of domperidone (see section 4.8 Adverse effects (Undesirable effects)). 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 domperidone affects them.
4.8 ADVERSE EFFECTS (UNDISIRABLE EFFECTS)

Clinical Trial Data

The safety of domperidone was evaluated in 1221 patients with gastroparesis, or symptoms of it in 45 clinical trials included in the safety database. All patients were ≥ 15 years old and received at least one dose of oral domperidone (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 Reactions (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

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Domperidone (n = 1221) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2.5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.6</td>
</tr>
<tr>
<td>Libido Decreased/Loss of Libido</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5.6</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.5</td>
</tr>
<tr>
<td>Akathisia</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Breast Enlargement/Gynaecomastia</td>
<td>5.3</td>
</tr>
<tr>
<td>Breast Tenderness</td>
<td>4.4</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>3.3</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>2.9</td>
</tr>
<tr>
<td>Breast Pain</td>
<td>2.3</td>
</tr>
<tr>
<td>Menstruation Irregular</td>
<td>2.0</td>
</tr>
<tr>
<td>Lactation Disorder</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.9</td>
</tr>
</tbody>
</table>
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% of Domperidone-Treated Patients in 45 Clinical Trials**

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Domperidone (n = 1221) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0.2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>0.7</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
</tr>
<tr>
<td>Breast Discharge</td>
<td>0.8</td>
</tr>
<tr>
<td>Breast swelling</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Postmarketing Data**

The adverse reactions are ranked by frequency, using the following convention:

- **Very common:** > 1/10
- **Common:** > 1/100, < 1/10
- **Uncommon:** > 1/1,000, < 1/100
- **Rare:** > 1/10000, < 1/1000
- **Very rare:** < 1/10000 including isolated reports
<table>
<thead>
<tr>
<th>Immune system disorder</th>
<th>Very rare</th>
<th>anaphylactic reactions including anaphylactic shock; angioneurotic oedema; allergic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorder</td>
<td>Uncommon</td>
<td>increased prolactin levels</td>
</tr>
<tr>
<td>Psychiatric system disorders</td>
<td>Uncommon</td>
<td>nervousness</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>agitation</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>dry mouth; headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>insomnia; dizziness; thirst; lethargy; irritability</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>extrapyramidal side effects</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>convulsion; somnolence</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
<td>diarrhoea; regurgitation; appetite disorder; nausea; heartburn; constipation</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>urticaria; pruritus; rash</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Rare</td>
<td>galactorrhoea; gynaecomastia; amenorrhoea</td>
</tr>
<tr>
<td>Urinary system disorders</td>
<td>Uncommon</td>
<td>Pollakiuria; dysuria</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Uncommon</td>
<td>Oedema; palpitations</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Sudden Cardiac Death*, Serious Ventricular Arrhythmias* (see section 4.4 Special warnings and precautions for use)</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>Uncommon</td>
<td>Muscle spasms; asthenia</td>
</tr>
<tr>
<td>Other</td>
<td>Uncommon</td>
<td>Conjunctivitis; stomatitis; drug intolerance</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>liver function test abnormal; cholesterol</td>
</tr>
</tbody>
</table>

*Based on epidemiology data
During long-term studies with domperidone there have been reports of adverse effects possibly related to increases in serum prolactin (see section 4.4 Special warnings and precautions for use). These effects include: Gynaecomastia, breast tenderness, swelling of the breasts, irregular menses, amenorrhoea, a decrease or loss of libido, breast secretion and lactation. These effects occurred in patients who received up to 120 mg per day in four divided doses.

Extrapyramidal disorder occurs very rarely, and when seen occurs primarily in young children (see section 4.4 Special warnings and precautions for use).

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

**Reporting suspected adverse effects**


**4.9 OVERDOSE**

**Symptoms**

Overdose has been reported primarily in infants and children. Symptoms of overdosage 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. Anticholinergics, antiparkinson drugs may be useful in controlling extrapyramidal reactions.

The patient should be observed closely and supportive measures employed.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Domperidone is a dopamine antagonist with antiemetic properties similar to those of metoclopramide and certain neuroleptic drugs. Unlike these drugs, however, domperidone does not readily cross the blood-brain barrier. It seldom causes extra-pyramidal side effects, but does cause a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone, which lies in the area postrema and is regarded as being outside the blood brain barrier. Animal studies have shown that domperidone has no effect on plasma concentrations of homovanillic acid, a metabolite of dopamine. It also antagonises the behavioural effects of dopamine much more effectively when administered intracerebrally than when given systemically. These findings, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in humans have shown intravenous and oral domperidone to: increase the duration of antral and duodenal contractions; increase the gastric emptying of liquids and semi solids in healthy subjects and in patients in whom it was delayed; increase lower oesophageal sphincter pressure in healthy subjects. Domperidone has 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 therapeutic doses (10 or 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 was 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. The QT prolongation observed in this study when domperidone was administered according to the recommended dosing is not clinically relevant.

Clinical trials

No data available.
5.2 PHARMACOKINETIC PROPERTIES

Absorption

Domperidone is rapidly absorbed following intramuscular and oral administration with peak plasma concentrations occurring at approximately 10 and 30 minutes, respectively.

Systemic bioavailability of intramuscular domperidone is about 83% whereas that of oral domperidone is 13 to 17%. The low oral bioavailability is probably due to ‘first-pass’ gut wall and hepatic metabolism. Oral bioavailability is decreased by prior administration of cimetidine or sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

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 with low brain concentration. Small amounts of drug cross the placenta in rats and the drug is excreted in the breast milk of this species.

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 (see section 4.5 Interactions with other medicines and other forms of interactions).

Excretion

Urinary and faecal excretion amounts to 31 and 66%, respectively, of the oral dose. The proportion of the drug excreted unchanged is small (approximately 1% of urinary excretion and 10% of faecal 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

Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3 Contraindications). In subjects with mild hepatic impairment (Pugh score 5 to 6, Child-Pugh rating A), limited data indicate that the pharmacokinetics of domperidone are not significantly altered. In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC, Cmax and terminal elimination half-life of domperidone were substantially increased; the unbound fraction of domperidone was increased by 25%. Subjects with severe hepatic impairment were not studied (see section 4.3 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 sections 4.4 Special warnings and precautions for use and 4.2 Dose and method of administration).

Paediatric Patients

No pharmacokinetics data are available in this population.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

See section 4.4 Special warnings and precautions for use - Prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Lactose monohydrate
- maize starch
- microcrystalline cellulose
- povidone
- magnesium stearate
- sodium lauryl sulfate
- colloidal anhydrous silica

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
6.5 NATURE AND CONTENTS OF CONTAINER

APO-Domperidone Tablet
Blister Pack (PVC/Aluminium) of 25, 30 or 100 tablets (AUST R 242333).

APO and APOTEX are registered trade marks of Apotex Inc.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Domperidone maleate is a white or almost white powder; it is very slightly soluble in water or ethanol, sparingly soluble in dimethylformamide and slightly soluble in methanol.

Chemical structure

![Chemical structure of Domperidone Maleate](image)

Chemical Name: 5-Chloro-1-[6-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one hydrogen (Z)-butenedioate.

Molecular Formula: $C_{26}H_{28}ClN_5O_6$

Molecular Weight: 542.0

CAS number 83898-65-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30 May 2016
## Summary table of changes

<table>
<thead>
<tr>
<th>Section Changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>Reformatted product information; minor editorial changes</td>
</tr>
<tr>
<td>4.3, 4.4, 4.5</td>
<td>Addition safety information in Contraindications, Warnings and Interactions sections</td>
</tr>
</tbody>
</table>