PRODUCT MONOGRAPH

[Pr]AVA-DOMPERIDONE

(Domperidone Maleate tablets)

10 mg domperidone

Modifier of Upper Gastrointestinal Motility

Avanstra Inc.
10761 – 25th street NE
Suite 110, Calgary, Alberta
T3N 0A4
Canada

Date of Revision:
April 28, 2012

Control No. 154230

PRODUCT MONOGRAPH

[Pr]AVA-DOMPERIDONE
Domperidone maleate tablets
10 mg domperidone

THERAPEUTIC CLASSIFICATION

Modifier of Upper Gastrointestinal Motility

ACTIONS AND CLINICAL PHARMACOLOGY

AVA-DOMPERIDONE (domperidone maleate) is a peripheral dopamine antagonist structurally related to the butyrophenones with antiemetic and gastroprokinetic properties.

Domperidone effectively increases esophageal peristalsis and lower esophageal sphincter pressure (LESP), increases gastric motility and peristalsis, enhances gastro-duodenal coordination and consequently facilitates gastric emptying and decreases small bowel transit time.

The mechanism of action of domperidone is related to its peripheral dopamine receptor blocking properties. Emesis induced by apomorphine, hydergine, morphine or levodopa through stimulation of the chemoreceptor trigger zone (situated outside the blood brain barrier) can be blocked by domperidone. There is indirect evidence that emesis is also inhibited at the gastric level, since domperidone also inhibits emesis induced by oral levodopa, and local gastric wall concentrations following oral domperidone are much greater than those of the plasma and other organs. Domperidone does not readily cross the blood-brain barrier and, therefore, is not expected to have central effects.

Domperidone elevates serum prolactin levels but has no effect on circulating aldosterone levels.

In humans, peak plasma levels of domperidone occur within 10 to 30 minutes following intramuscular injection and 30 minutes after oral (fasted) administration. Plasma concentrations two hours after oral administration are lower than following intramuscular injection, and this is likely the result of hepatic first-pass and gut wall metabolism. Peak plasma concentrations are 40 ng/mL following an i.m. injection of 10 mg, 20 ng/mL after a single 10 mg tablet, and 70 to 100 ng/mL after oral doses of 60 mg (tablets or oral drops). The half-life was calculated as approximately 7.0 hours in each case. The degree of human plasma protein binding was calculated from tritiated domperidone concentrations of 10 and 100 ng/mL as 91.8 and 93.0%, respectively.

The major metabolic pathways for domperidone in humans are hydroxylation and oxidative N-dealkylation, the products of which are hydroxydomperidone and 2,3-dihydro-2-oxo-1-H-benzimidazol-1-propionic acid, respectively. *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. After oral administration of 40 mg ^{14}C-domperidone to healthy volunteers, 31% of the radioactivity is excreted in the urine and 66% in the feces over a period of four days.

The relative bioavailability Avanstra Inc.'s domperidone 10 mg tablets and Motilium® 10 mg tablets of Janssen Pharmaceutica Inc. was compared. The study was a single dose (6 x 10 mg tablets) administered to each of 24 fasted healthy male volunteers in a balanced randomized 2-way (crossover design). Blood samples were collected pre-dose and at the following times after dosing, 10, 20, 30 and 45 min. and 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours.

Blood samples were determined according to the HPLC method with UV detection. The results of this biostudy are summarized in the following table:

Mean (CV%) pharmacokinetic parameters domperidone

	AUC 0-t ng.h/mL	**Tmax h**	**Cmax ng/mL**	**AUC inf ng.h/mL**
Avanstra inc.	210.73	0.91	71.72	223.86
Janssen	217.10	0.83	74.76	231.49

Based on the bioavailability study, Avanstra inc.'s domperidone 10 mg tablets are judged to be comparable in both rate and extent of absorption to Janssen's formulation (Motilium ®) domperidone 10 mg tablets.

INDICATIONS AND CLINICAL USE

AVA-DOMPERIDONE (domperidone maleate) is indicated in the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis.

AVA-DOMPERIDONE may also be used to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents.

CONTRAINDICATIONS

AVA-DOMPERIDONE (domperidone maleate) is contraindicated in patients with known sensitivity or intolerance to the drug.

Domperidone should not be used whenever gastrointestinal stimulation might be dangerous, i.e., gastrointestinal hemorrhage or mechanical obstruction or perforation.

AVA-DOMPERIDONE (domperidone maleate) is also contraindicated in patients with a prolactin-releasing pituitory tumour (prolactinoma)

The co-administration of domperidone with ketoconazole is contraindicated (see Warnings and Precautions, Cardiovascular section and Drug Interactions section).

WARNINGS

Serious Warnings and Precautions

Cardiovascular adverse events:
Recent epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (*see Adverse Reactions*). The risk may be higher in patients older than 60 years or in patients taking a daily dose of more than 30 mg.

Based on the above-mentioned reports of serious ventricular arrhythmias and sudden cardiac death, caution should be exercised when using domperidone with:

- drugs which prolong QT intervals, in patients who have existing prolongation of cardiac conduction intervals, particularly QTc, and in patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.
- CYP3A4 inhibitors (see below) which may increase plasma levels of domperidone (*see Drug Interactions).*

Domperidone should be initiated at **the lowest possible dose,** which may be adjusted upward with caution to achieve the desired effect as needed. The expected benefit of an increased dose should outweigh the potential risks (*see Dosage and Administration, Drug Interactions, Adverse Reactions*).

Cardiovascular:
In an interaction study, when domperidone was administered with ketoconazole, an increase in the QT interval was observed. The increase was greater than that observed when ketoconazole was a administered alone (See Drug Interactions section below). Co-administration of ketoconazole with domperidone is contraindicated. QT prolongation was not observed at oral doses of domperidone of up to 160 mg/day, i.e., twice the

maximum recommended daily therapeutic dose. **It is noteworthy that cardiac arrhythmia and death were reported following very high parenteral doses of domperidone.**
These results should be considered when domperidone is prescribed with other CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors, grapefruit juice), which may increase plasma levels of domperidone. Consideration need to be given also when domperidone is co-administered with drugs associated with QT prolongation ot *torsade de pointes* (e.g. drugs in classes such as antiarrhythmics, quinolone antibiotics, antipsychotics, 5-HT_3 antagonists, beta-2 adrenoreceptor agonists, azole antifungals, macrolides and analogues, antimalarials, SSRIs, tri/tetracyclic antidepressants), especially in patients at risk for *torsade de pointes.*

Prolactin levels:
Dopamine receptor blocking agents elevate prolactin levels; the elevation persists during chronic administration. 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 these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, 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 dopamine receptor blocking agents,. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence is considered too limited to be conclusive at this time.

Renal:
In patients with severe renal insufficiency (serum creatinine > 6 mg/100 ml or > 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 a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Generally, patients on prolonged therapy should be reviewed regularly.

Use in Pregnancy:
While animal studies have not shown drug related teratogenic or primary embryotoxic effect on animal fetuses (see Toxicology), comparable studies have not been performed in pregnant women. For this reason, AVA-DOMPERIDONE (domperidone maleate) should not be used in pregnant women unless the expected benefit outweighs the potential hazard.

Use During Lactation:

Domperidone is excreted in breast milk in very low concentrations. Therefore nursing in not recommended for mothers taking AVA-DOMPERIDONE (domperidone maleate) unless the expected benefits outweigh any potential risk.

Use in Children:
The safety and efficacy of domperidone in children have not been established, therefore, domperidone should not be used in children.

PRECAUTIONS

In the event that the patient develops galactorrhea and/or gynecomastia, withdrawal of the drug will result in alleviation of these symptoms.

DRUG INTERACTIONS

In vivo interaction studies have shown that ketoconazole strongly inhibits the CYP3A4-dependent metabolism of domperidone. Pharmacokinetic studies showed 3-10 fold increase in the area under curve (AUC) and the peak concentration (Cmax) of domperidone when ketoconazole was co-administered.

This co-administration resulted also in a prolongation of the QT interval (maximum of 10-20 msec) which was greater than the prolongation observed with ketoconazole alone. QT prolongation was not observed at oral doses of domperidone of up to 160 mg/day, i.e., twice the maximum recommended daily therapeutic dose. It is important note that cardiac arrhythmia and death were reported following high parenteral doses of domperidone.

Results of the interaction study should be considered when domperidone is prescribed with CYP3A4 inhibitors (which may increase plasma levels of domperidone) or with drugs that can cause QT prolongation or *torsade de pointes*, especially in patients at risk for *torsade de pointes* (see Contraindications, Warnings and Precautions, Cardiovascular sections).

The concomitant administration of anticholinergic drugs may compromise the beneficial effects of AVA-DOMPERIDONE.

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. Examples of CYP3A4 inhibitors include the following:

- azole antifungals;
- macrolide antibiotics;
- HIV protease inhibitors; and
- nefazodone.

Since domperidone enhances gastric and small intestinal motility, it may accelerate absorption of drugs from the small bowel while slowing absorption of drugs taken up from the stomach, particularly those with sustained release or enteric-coated formulations.

Care should be exercised when domperidone is administered in combination with MAO inhibitors.

The concomitant administration of domperidone maleate with antacids or H_2-receptor blockers does not decrease the absorption of domperidone maleate.

Use in Patients with Hepatic Impairment
Since domperidone is highly metabolized in the liver, it should be used with caution in patients with hepatic impairment.

Use in Patients with Renal Impairment
In patients with severe renal insufficiency (serum creatinine > 6mg/100mL, i.e.,> 0.6mmol/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. In patients with renal insufficiency, the dosing frequency should be reduced (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

In clinical studies with oral domperidone the overall incidence of side effects was <7%. Some of these side effects are an extension of the dopamine antagonist properties of domperidone. Most side effects resolve spontaneously during continued therapy or are easily tolerated. The more serious or troublesome side effects (galactorrhea, gynecomastia, menstrual irregularities) are dose-related and gradually resolve after lowering the dose or discontinuing of therapy.

Central Nervous System: 4.6%; dry mouth (1.9%), headache/migraine (1.2%), insomnia, nervousness, dizziness, thirst, lethargy, irritability (all <1%).

Gastrointestinal: 2.4%; abdominal cramps, diarrhea, regurgitation, nausea, changes in appetite, heartburn, constipation (all <1%).

Endocrinological: 1.3%; hot flushes, mastalgia, galactorrhea, gynecomastia, menstrual irregularities.

Mucocutaneous: 1.1%; rash, pruritus, urticaria, stomatitis, conjunctivitis.

Urinary: 0.8%; urinary frequency, dysuria.

Cardiovascular: 0.5%; edema, palpitations.

Musculoskeletal: 0.1%; leg cramps, asthenia.

Miscellaneous: 0.1%; drug intolerance.

Laboratory Parameters: elevated serum prolactin, elevation of SGOT, SGPT and cholesterol (all <1.0%).

Extrapyramidal phenomena are rare in adults; they reverse spontaneously as soon as treatment is stopped. When the blood-brain barrier is immature (as in infants) or impaired, the possible occurrence of neurological side effects cannot be excluded.

Post-Market Adverse Drug Reactions

Cardiovascular: torsade de points, serious ventricular arrhythmias (frequency unknown), sudden cardiac death (frequency unknown).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Symptoms

Based on the pharmacological properties of domperidone, symptons of overdosage may include CNS effects (such as drowsiness, disorientation and extrapyramidal reactions, especially in children) and cardiovascular effects (arrythmia, hypotension) might possibly occur.

Treatment

Anticholinergic, anti-parkinsonian drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. There is no specific antidote to domperidone but in the event of overdosage, gastric lavage as well as the adminstration of activated charcoal may be useful. Close observation and supportive therapy are recommended. Symptoms are self-limiting and usually disappear within 24 hours.

DOSAGE AND ADMINISTRATION

Important considerations:

- Domperidone should be initiated at the lowest possible dose and adjusted upward, with caution, to achieve the desired effect as needed.
- The expected benefit of an increased dose should outweigh the potential risks.
- Recent post-market epidemiological studies have shown that the risk of serious ventricular arrhythmias or sudden cardiac death may be higher in patients older than 60 years of age or in patients taking a daily dose of more than 30 mg. (*see*

Warnings-Serious Warnings and Precautions, Drug Interactions, Adverse Reactions).

- Caution must be exercised in Parkinson patients in whom the initial recommended doses exceed 30 mg per day.

The below dosage recommendations are based on earlier clinical trial data, prior to the availability of these epidemiological study results.

Upper Gastrointestinal Motility Disorders:
The usual dosage in adults is 10 mg orally 3 to 4 times a day, 15 to 30 minutes before meals and at bedtime if required. In severe or resistant cases the dose may be increased to a maximum of 20 mg 3 to 4 times a day.

Nausea and Vomiting Associated with Dopamine Agonist Antiparkinsonian Agents:
The usual dosage in adults is 20 mg orally 3 to 4 times a day. Higher doses may be required to achieve symptom control while titration of the antiparkinsonian medication is occurring.

Dosage Consideration

Patient with renal impairment:
Since very little unchanged drug is excreted via the kidneys, it is unlikely that a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated adminstration, 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. Generally, patients on prolonged therapy should be reviewed regularly (see Warnings and Precautions, Renal section).

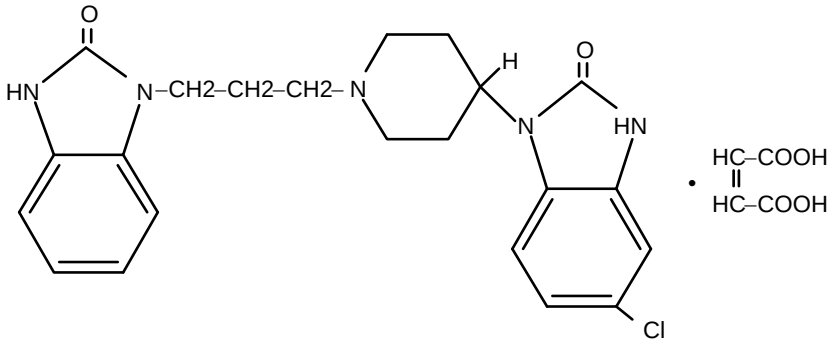
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Domperidone Maleate

Chemical Name: 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl) propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one(Z)-2-butenedioate (1:1)

Structural Formula:



Molecular Formula: $C_{22}H_{24}N_5O_2Cl \cdot C_4H_4O_4$

Molecular Weight: 541.99 g/mol

Description: Domperidone maleate is a white to off white crystalline powder, soluble in N,N-dimethylformamide, and insoluble in water with a melting range of 223-231°C.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15-30°C. Protect from light. Unit dose strips should be stored between 15-25°C and protected from high humidity and light.

AVAILABILITY OF DOSAGE FORMS

AVA-DOMPERIDONE (domperidone maleate) is available as:

10 mg - round, plain-coated, biconvex white tablet, engraved "rph D51" on one side and plain on the other side containing 12.72 mg of domperidone maleate equivalent to 10 mg of domperidone.

Supplied: Bottles of 500.

Non-medicinal ingredients:

Cornstarch, croscarmelose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, sodium docusate 85%-sodium benzoate 15% and, titanium dioxide, triacetin.

PHARMACOLOGY

AVA-DOMPERIDONE (domperidone maleate) is a dopamine antagonist which does not readily cross the blood-brain barrier and exerts its primary effect on peripheral dopamine receptors.

While ^{3}H-domperidone binded specifically and selectively to mouse and rat striatal dopamine receptors *in vitro,* domperidone, administered *in viv,* showed no displacement of ^{3}H-spiperone in rat brain dopaminergic areas and did not increase rat brain homovanillic acid (HVA) concentrations. Accordingly, domperidone had no effect on behaviour, conditioned reflexes, intracranial self-stimulation or EEG tracings at concentrations up to 100 times in excess of the antiemetic dose. These studies indicate that domperidone does not cross the blood brain barrier.

In baboons and in the dogs, domperidone given intravenously produced a dose-dependent increase in lower esophageal sphincter pressure. Gastric relaxation studies in the dog showed that, at i.v. doses of 1 and 3 mg/kg, domperidone increased gastric tone. In the dog, dopamine-induced gastric relaxation was prevented by domperidone i.v. at a dose of 0.3 mg/kg. In the isolated guinea pig stomach-duodenum preparation, dopamine and noradrenaline produced gastric relaxations which could be antagonized in a dose-dependent manner by domperidone. Domperidone also increased the amplitude and decreased the frequency of peristaltic waves in the same *in vitro* preparation. In female dogs, domperidone (1 mg/kg) increased the antral contraction pressure while decreasing the frequency. A dose of 0.3 mg/kg i.v. domperidone also prevented both the gastric relaxation and the reduced amplitude of phasic activity induced by dopamine. Domperidone also improved antroduodenal coordination (defined as the propagation of peristaltic waves from the stomach to duodenum) in the isolated guinea pig stomach-duodenum-preparation. In the dog, intravenous administration of 0.31 mg/kg domperidone resulted in an increase in antroduodenal coordination from 35% to 80%. In dogs, 0.35 and 0.7 mg/kg i.v. domperidone significantly increased the distension of the pyloric sphincter. Gastric emptying studies performed in the dog showed that domperidone 0.4 mg/kg i.v significantly decreased the stationary phase of a solid meal by 50% and also increased the emptying rate. Domperidone also reversed the dopamine-induced prolongation of the stationary phase of both solid and semi-solid meals.

Domperidone was found to be a potent inhibitor of apomorphine-induced emesis in the dog: after a s.c. injection of 0.31 mg/kg apomorphine, the ED_{50} for domperidone was 0.007 mg/kg s.c. and 0.031 mg/kg p.o. Domperidone was also highly effective in

preventing emesis induced by hydergine, levodopa and morphine but ineffective in preventing copper sulfate induced emesis.

In rats, domperidone induced a significant rise in plasma prolactin levels. This effect could be reversed by apomorphine. In rats treated with 0.25 mg/kg/day domperidone for 14 days, prolactin levels were found to be significantly higher than those of untreated animals.

TOXICOLOGY

Acute Toxicity:

Species		Route of Administration	LD_{50} (mg/kg) 7 days
Mice	M	i.v.	56.5 (43.2-73.8)
	F	i.v.	56.8 (43.5-74.2)
Rats	M	i.v.	56.3 (43.1-73.6)
	F	i.v.	68.8 (52.6-89.9)
Guinea-pigs	M	i.v.	42.9 (32.8-56.1)
	F	i.v.	44.4 (34.0-58.0)
Dogs	M & F	i.v.	42.7 (32.7-55.9)
Mice	M	p.o.	>1280
	F	p.o.	>1280
Rats	M	p.o.	>1280
	F	p.o.	>1280
Guinea-pigs	M	p.o.	796 (424-1493)
	F	p.o.	>1280
Dogs	M &F	p.o.	>160
Dogs	M & F	s.c.	>160

Signs of toxicity:

1. Following i.v administration:
in mice: ptosis (≥ 20 mg/kg), sedation (≥ 40 mg/kg), tremors and convulsions (> 80 mg/kg).
in rats: ptosis, sedation and catalepsy (≥ 5 mg/kg), convulsions (≥ 80 mg/kg).
in guinea pigs: ptosis and sedation (≥ 20 mg/kg) and dyspnea before death at 40 mg/kg.
in dogs: ataxia, sedation and vomiting starting at 10 mg/kg.

2. Following oral administration:
in mice: ptosis, sedation, and occasionally ataxia (≥ 320 mg/kg).
in rats: ptosis, sedation and catalepsy (≥ 40 mg/kg).
in guinea pigs: ptosis sedation and occasionally diarrhea (≥ 320 mg/kg).
in dogs: vomiting at 160 mg/kg.

3. Following subcutaneous administration:
in dogs: sedation and cataleptic immobility.

SUBACUTE TOXICITY

Intravenous toxicity study in Wistar rats (3 weeks)
Rats (10 M, 10 F/group) received intravenously 0, 2.5, 10 and 40 mg/kg domperidone once a day, six days a week. There was no effect on mortality, behaviour and appearance. At the high dose, food consumption and body weight gains were significantly lower in male animals only.

There was an increase of segmented heterophils and a decrease of lymphocytes in high dose animals. Serum analysis were normal except for an increase in alkaline phosphatase in all dosed female groups and an increase of haptoglobin in high dosed males and females.

At 40 mg/kg, a moderate to strong irritation of the tail with progressive necrosis was noted in both males and females. Also at this high dose, stimulation of the mammary glands was seen in several females. A decrease in spleen weight was noted in all groups of dosed males and females. At high dose, most of the organ weights decreased, especially in male animals where a lower terminal body weight was noted. Histopathology revealed the following: reduced number of corpora lutea in the ovary at 40 mg/kg, reduced eosinophilic infiltration of the uterine wall and more folded uterine mucosa at 40 mg/kg, mucification of the vagina at 40 mg/kg and rarely at lower dosages, atrophied and female aspect of the mammary gland in dosed males and glandular development with secretion in the dosed females in a dose-related fashion, more extended chromophobe tissue of the hypophysis at all dosages.

Intravenous toxicity study in Beagle dogs (3 weeks)

Dogs (3 M, 3 F/group) received intravenously 0, 1.25, 5 and 20 mg/kg domperidone once a day, six days a week. There was no effect on mortality. Emesis and reduced appetite were seen at the 20 mg/kg dose. Behaviour and appearance were otherwise unaffected. Body weight remained comparable between control and dosed groups. Heart rate, ECG and blood pressure remained normal in all groups.

At the high dose, there was a marginal decrease in hematocrit and hemoglobin. Serum analysis and urinalysis remained normal throughout the study.

Organ weights remained normal in all groups except for a slight increase in relative liver weight at high dose and a slight decrease in absolute and relative adrenal weight at all doses. Histologically, both liver and adrenals were normal and comparable to controls. The following changes were seen histopathologically: reduced or absent spermatogenesis at high dose, atrophy of the prostate high dose, degranulation of the erythrosinophilic cells of the hypophysis at 5 and 20 mg/kg.

Oral toxicity study in Wistar rats (15 weeks)
Rats (10 M, 10 F/groups) received orally 0, 10, 40 and 160 mg/kg domperidone mixed in the diet. At the high dose, a decrease in appetite and weight gain was observed as well as two deaths, both unrelated to drug administration. Food consumption was increased in low and medium dose females. Hematology and serum analysis were normal in all groups.

Urinalyses were normal except for a decrease in creatinine in all dosed females. Stimulation of the mammary glands was seen in all dosed females. Organ weights were comparable in all groups with following exceptions: increase in absolute liver weight in low dose females where body weight increased. At the high dose, the absolute weight of several organs was significantly lower than in the control group, due to lower total body weight in this group. Histopathology revealed the following changes: mucification of the vaginal epithelium, reduction in number of corpora lutea in all dosed females, female aspect with sometimes fluid secretion in the mammary gland of dosed male animals, marked development of grandular tissue filled with secretion in all dosed females, increased chromophobe or erythrosinophilic tissues and less active gonadotrophs in the hypophysis.

Oral toxicity study in Beagle dogs (3 months)
Dogs (3 M, 3 F/group) received orally 0, 2.5, 10 and 40 mg/kg domperidone once a day, six days a week. All animals survived the experiment. At the high dose, there was a decrease in appetite, and ocular discharge and ptosis were noted. Food consumption decreased at high dose, and there was a persistent body weight loss. Heart rate, ECG and blood pressure remained normal in all groups.

Hematological parameters were normal except for a decrease in hematocrit, hemoglobin and red blood cells at the high dose. Serum analysis and urinalysis remained normal in all groups. Organ weights were normal except for a dose-related increase of the relative

liver weight in all dosage groups. At the high dose, an increase of most relative organ weights was expected from decreased total body weight. The following histopathological observations were noted: desquamation and some degeneration of germial epithelium with no spermatogenesis in 2/3 males at high dose; prostatic atrophy at 10 and 40 mg/kg; some thymus involution in 2/3 high dosed females; more extended erythrosinophilic tissue in the hypophysis in high dosed males and mid and high dosed females.

CHRONIC TOXICITY

Oral toxicity study in Wistar rats (6-12-18 months)

Four groups of 10 male and 10 female rats received domperidone orally each day, seven days a week, at doses of 0, 10, 40 and 160 mg/kg during 6, 12 and 18 months, so that a total of 240 animals were used throughout the course of the study.

No dose-related effects on the mortality rate were observed in the 6, 12, and 18 month studies. The only effect on behaviour was an increased appetite observed in the 10 mg/kg dosed females, and also in the 40 mg/kg females, but to a lesser extent. This resulted in adipositas in several animals, especially in the 12 and 18 months studies. Stimulation of the mammary glands was noticed at all dose levels in the females and also in most of the high dosed males in the 18 month study. Food consumption was decreased at high dose for both males and females in the 6 month study, and in males of the 12 and 18 month studies. Increased food consumption was observed in the 10 mg/kg females of the 6, 12 and 18 month studies. Decreased food consumption correlated with decreased body weight at 160 mg/kg in males and females (6 months) and in males (12 months). Hematology and biochemistry were normal except for the following findings: slight increase of non-segmented heterophils in the 40 and 160 mg/kg dosed females (12 months), marginal increase of monocytes in the 40 and 160 mg/kg dosed females (18 months), marginal increases of inorganic phosphorus in dosed females (12 months). Urinalysis was normal. Most of the necropsy findings occurring in dosed as well as undosed animals were related to aging process: pneumonia, lung abscesses, alopecia, thymus involution. Drug administration caused stimulation of the mammary glands in all dosed females of the 6, 12 and 18 month studies, and in several of the 160 mg/kg dosed males of the 18 month study. No adverse effect on organ weight was noted.

Histopathological changes were described as follows:

- enhanced prostatitis in many dosed rats at all dosages, but not at 10 mg/kg in the 6 month experiment;
- progestational aspect of the female genital tract at all dosages (6 and 12 month experiments);
- female aspect or atrophy of the mammary gland in males at all dosages;
- mammary glands stimulation in the females at all dosages after 6 and 12 months and at 160 mg/kg after 18 months;
- inverted or irregular gradient of fat in the adrenals of males at 160 and 40 mg/kg after 6 and 12 months, and at 160 mg/kg after 18 months in the males; absence of fat gradient at 160 mg/kg and 40 mg/kg in the females after 6 months;

- chronic stimulation of the chromophobe or erythrosinophilic tissues of the hypophysis at all dosages.

Oral toxicity study in Beagle dogs (12 months)
Four groups of 3 male and 3 female dogs received domperidone orally each day, seven days a week, at dosages of 0, 2.5, 10 and 40 mg/kg for a period of 12 months.

There was no mortality during the study, except for 1 animal at 40 mg/kg which died during week 8 with gastro-enteritis and peritonitis. This death was not considered to be drug related. Behaviour and appearance were unaffected, except for some temporary ocular lesions believed to be of an infectious origin which regressed during the study, and were observed in a few dogs. Some decreased food consumption was observed at the high dose, causing a lower terminal body weight. ECG, heart rate and blood pressure remained within normal values. Hematological values remained normal except for a slight decrease of hematocrit, hemoglobin and red blood cells at 10 and 40 mg/kg and slight increase in monocytes and thrombocytes at 40 mg/kg. Serum analysis was normal in all groups except for a marginal to moderate increase of haptoglobin in the 10 and 40 dosage groups.

Urinalysis remained normal throughout the study. Gross pathology changes were limited to a small sized prostate in the 10 and 40 mg/kg dosed males. Organ weights were normal except at high dose, where the increased relative liver weight was considered a possible drug and dose related effect.

Histopathological changes were described as follows:
Testis: A tendency to more marked desquamation or to a looser germinal epithelium at 10 and 40 mg/kg, two dogs at these dosages showing more extended degeneration changes with impairment of spermatogenesis.

Prostate: Atrophy and/or fibrosis of the prostate characterized the 40 mg/kg dosed males and to a lesser extent the 10 mg/kg dosed one.

Eyes: Keratitis was noted in 10 and 40 mg/kg dosed animals; these changes were explained by the lowered resistance of these animals to some kennel infection at the time of the experiment.

CARCINOGENICITY STUDIES

Oral carcinogenicity study in Albino Swiss mice
Four hundred Albino Swiss mice were divided into four groups of 50 males and 50 females. Each group received orally through the drinking water for 18 months, 0, 6.25 ppm (2.5 mg/kg body weight/day), 25 ppm (10 mg/kg/day) or 100 ppm (40 mg/kg/day) domperidone. No dose related effects on overall survival rate or on the time at which mortalities occurred were observed. There were no dose-related effects on health, appearance or behaviour. No dose-related effects on gross pathology were seen.

Histopathological examinations revealed no difference between groups with regard to the number of tumor-bearing mice. The incidences of the various tumor types in both males and females were comparable for each dosage group except for a dose related increase in mammary carcinomas which was significant in the high dose females. The latter finding was expected for a dopamine antagonist given at high dosages.

Oral carcinogenicity study in Wistar rats
Four hundred Wistar rats were divided into four groups of 50 males and 50 females. Each group received orally admixed in the diet for 24 months, 0, 2.5 mg/100 g food/day (2.5 mg/kg bady weight/day), 10 mg/100 g food/day (10 mg/kg body weight/day) and 40 mg/100 g food/day (40 mg/kg body weight/day) domperidone. No dose-related effects on survival rate were noticed and no dose-related effects on health, behaviour and physical appearance were observed. No dose-related effects on gross pathology were seen.

Histopathological examinations revealed that no statistical differences could be noted on the total incidence of tumor bearing rats when the various dosage groups of the males and females were compared. The incidence of various tumor types was not significantly different from the control values except for the males of the high dosage group which showed a marginally increased incidence of pituitary adenomas. In the high-dosed females, there was a slight tendency towards an increase in mammary carcinomas. The number of thyroid adenomas found in the mid-dosed females was quite high, but this was not so in the high-dosed females. These findings on pituitary and mammary glands tumourigenesis were expected for a dopamine-antagonist at high dosages.

Mutagenicity Studies:
Domperidone was shown to have no mutagenic potential in the following models: dominant lethal test in male and female mice, micronucleus test in mice, *Salmonella typhimurium* (Ames's test), *in vitro* chromosomal aberrations in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*.

REPRODUCTION AND TERATOGENICITY STUDIES

A) Oral Embryotoxicity and Teratogenicity Studies in the Rat
Oral embryotoxicity and teratogenicity study in Wistar rats (Segment II)
Eighty female Wistar rats were divided in 4 groups of 20 animals each and received orally 0, 10, 40 and 160 mg/kg domperidone each day from day 6 to day 15 of gestation. Pregnancy rate was 65% in the high dose group as compared to 100% in the lower dosage groups and 90% in the control group. Administration of domperidone had no effect on the following parameters: number of implantations, pregnancies and pups, litter size and weight at birth, number of resorptions, live and dead fetuses, number of distribution of live, dead and resorbed embryos. No embryotoxic or teratogenic effects were seen.

Oral embryotoxicity and teratogenicity study in Wistar rats (Segment II)

Eighty female Wistar rats were divided in 4 groups of 20 animals each and received 0, 5, 20 or 80 mg/kg domperidone p.o. each day from day 6 to day 15 of gestation. Pregnancy rate was 80% at low dose, 100% at mid dose and 95% at high dose, compared to 95% in the control group. There was no embryotoxic or teratogenic effect and no effect on number of implantations, pregnancies and pups, litter size and weight at birth, number of resorptions, live and dead fetuses, number and distribution of live, dead and resorbed embryos.

Oral embryotoxicity and teratogenicity study in Wistar rats (Segment II)
Eighty female Wistar rats were divided in 4 groups of 20 animals each and received by gavage 0, 160, 320 and 640 mg/kg domperidone each day from day 6 to day 15 of gestation. Body weight gain was much lower in all dosage groups and was correlated to lower food consumption in these groups.

One female at 320 and 2 females at 640 mg/kg died during the study. These females were not pregnant and autopsy failed to reveal the cause of death. Rates of pregnancy were 95% in the control group, 85% in the 160 mg/kg group, 20% in the 320 mg/kg group and 25% in the 640 mg/kg groups. The percentage of resorptions increased with dose and was 100% in the high dose group. Litter size and weight of pups at delivery were also decreased in the low and mid dose groups,. No drug related teratogenic effect was detected. However, at these high dosages, there was no evidence of maternal toxicty.

Oral three generation reproduction study in Wistar rats Exp. No. 913
Forty young and healthy adult males and one hundred and twenty young and healthy virgin females (Wistar rats) were used as the F_0 generation. The animals were divided into 4 groups of equal size and dosed with domperidone at 0, 10, 40 and 160 mg/100 g food. The F_0 generation was dosed from the age of 3 months onwards, i.e., from day 0 of mating and further through breeding and weaning. A total of 20 inseminated females per dosage group (i.e., 80/120) were followed during their gestation. Their progeny on days 1, 4, 14 and 21. After weaning at day 21 and a further $2^1/_2$ months growing period, a second generation was bred from the F_1 litter. The males and the females of the second generation were randomly chosen: at least 10 males and 20 females per dosage group. Upon reaching sexual maturity at 3 months, one was coupled with two females by excluding brother-sister mating. The inseminated females were isolated until 3 weeks after parturition. The pups of the F_2 litter were weighed on days 1, 4, 14 and 21. After weaning at day 21 and a further $2^1/_2$ months growing period, a third generation was bred from the F_2 litter in the same way as described above. The males and females of the third generation were randomly chosen: at least 10 males and 20 females per dosage group. Upon reaching sexual maturity at 3 months, one male was coupled with two females by excluding brother-sister mating. The inseminated females were isolated until sacrifice at day 22 of gestation. All delivered F_3 pups were weighed.

The males and females of the second (F_1) and third (F_2) generations were dosed continuously at the same dose levels as the F_0 generation.

Body weight gain was lower in the high dosage group of the three generations, but only in the first generation was this difference significant. This correlated with a decreased food consumption in that same group. No mortality was recorded in each of the groups. No differences in pregnancy rates were observed between groups. The observed differences in gestation periods between groups in the first generation were not dose-related and were all within normal limits. No differences were seen in the second generation. There were some small differences between groups in litter size and number of live fetuses but all were considered to be within normal limits, except for the decrease seen in the high dosage group, which is attributed to maternal toxicity. The same applies to birth-weight, weight at 2 and 3 weeks and survival rate. There was no difference in abnormalities between treated and untreated groups.

B) Intravenous Embryotoxicity and Teratogenicity Study in the Rat

Intravenous embryotoxicity and teratogenicity study in Wistar rats

Eighty female Wistar rats were divided into 4 groups of 20 animals each and received intravenously 0, 2.5, 10 and 40 mg/kg/day from day 6 to day 15 of gestation. Body weight increase was normal and no mortality occurred in all groups. Pregnancy rates were respectively 95%, 100%, 95% and 85% in the control, low, mid and high dose groups, The percentages of live, dead and resorbed fetuses were respectively 97.2%, 0% and 2.8% in the control group, 94.8% 0% and 5.2% in the low-dose group, 92.1%, 0% and 7.9% in the mid-dose group, 90.5%, 0% and 9.5% in the high dose group, indicating a slight increase in resorptions with increasing dosages. No differences in abnormalities were seen between treated and untreated groups.

C) Oral Embroyotoxicity and Teratogenicity Studies in the rabbit

Oral embryotoxicity and teratogenicity study in New Zealand white rabbits

Sixty female New Zealand white rabbits were divided into three groups of 20 animals each and received 0, 10 and 40 mg/kg domperidone by gavage from day 6 through day 18 of gestation. There was one death at low dose and 9 deaths at the high dose. The cause of death was lobular pneumonia in 2 cases, enteritis in one case and pneumonia with mucoid enteritis in another case. Weight gain was apparent in all groups but was decreased in dosed animals. Rates of pregnancies were 85% in the control and low dose groups, and 70% in the high dose group. The average litter size was 6.2 in the control group, 5.7 in the low dose group and 5.5 in the high dose group. The percentage of live, dead and resorbed fetuses for all groups were respectively 83.9%, 0.8% and 15.3% (control group); 72.6%, 1.6% and 25.8% (low dose group); 76.6%, 2.6% and 20.8% (high dose group). Therefore the percentage of resorption increased in dosed groups. At resection the average birth weight of live pups at resection was 41.5 g (control), 40.7 g (low dose) and 36.3 g (high dose). The 24 hour survival rate of incubated pups was 75% in controls, 61.1% in low-dosed animals and 40.7% in high-dosed animals. No abnormalities were noted in any group.

In conclusion, it can be said that domperidone did not produce teratogenic effects at doses of 10 and 40 mg/kg.

There was, however, a slight increase in resorptions in dosed animals with evidence of maternal toxicity.

Oral embryotoxicity and teratogenicity study in New Zealand white rabbits
Sixty female New Zealand white rabbits were divided into three groups of 20 animals each and received 0, 5 and 20 mg/kg/day domperidone by gavage from day 6 through day 18 of gestation. There was no death in the control group, but three animals died in the 5 mg/kg groups and twelve died in the high dose group. Pregnancy rates were 60% for the control group, 70% for the low dose group and 40% for the high dose group.

The percentages of live, dead and resorbed foetuses were respectively 70.0%, 0% and 30% in the control group, 64.6%, 0% and 35.4% in the low dose group and 82.4%, 5.9% and 11.7% for the high dose group. At resection, the average birth weight of live pups was: 42.5 g (control), 39.0 g (5 mg/kg group) and 34.7 g (20 mg/kg group). Survival rate of of incubated pups, 24 hours after delivery was: 54.3% (controls), 52.4% (5 mg/kg), and 14.3% (20 mg/kg). Survival rate was significantly decreased at 20 mg/kg. No teratogenic effect was seen. Maternal toxicity is evident at 5 and 20 mg/kg as pregnancy rate decreased (20 mg/kg), mortality rate increased and weight gain decreased (5 and 20 mg/kg).

D) Intravenous Embryotoxicity and Teratogenicity Studies in the Rabbit
Intravenous embryotoxicity and teratogenicity study in New Zealand white rabbits
Sixty female New Zealand rabbits were divided into three groups of 20 animals each and received intravenously 0, 0.63 and 1.25 mg/kg from day 6 through day 18 of gestation. Survival rate in the dams was 100% in the control group, 85% at low dose and 100% at high dose. Three animals died in the low dose group. Body weight gains were comparable in all groups. Pregnancy rates were 100% in the control group. Pregnancy rates were 100% in the control group, 85% in the low dose group and 90% in the high dose group. Average litter size was comparable in all groups. The percentages of live, dead and resorbed fetuses for all group were respectively 90.2%, 0% and 9.8% for the control, 99.2%, 0% and 0.8% in the low dose group and 97.1%, 0% and 2.9% in the high dose group. The average birth weight of live pups was: 34.6 g (controls), 35.3 g (low dose), and 36.9 g (high dose). Survival rate of incubated pups 24 hours after delivery was: 77.7% (controls), 76.7% (low dose) and 76.5% (high dose). Domperidone administered under these conditions did not produce any embryotoxic or teratogenic effects.

Intravenous embryotoxicity and teratogenicity study in New Zealand white rabbits
Sixty female New Zealand white rabbits were divided into four groups of 15 animals each and received by the intravenous route 0, 0.63, 1.25 and 2.5 mg/kg from day 6 through day 18 of gestation. There were 3 of 15 deaths in the control group, 1 of 15 in the low dose group, 2 of 15 in the mid dose group and 8 of 15 in the high dose group. The decreased survival rate in the high dose group was significant. No difference in pregnancy rates was seen among the various groups. The average litter size was 4.9 in

control group, 3.9 (0.63 mg/kg group), 3.9 (1.25 mg/kg group) and 1.7 (2.5 mg/kg group). The number of live, dead and resorbed fetuses per female for all groups were respectively: 4.3, 0.6, 1.7 (controls), 3.8, 0.1, 0.3 (0.63 mg/kg), 3.8, 0.1, 1.7 (1.25 mg/kg) and 1.7, 0.0, 2.5 (2.5 mg/kg). At resection. the average birth weight of live pups was: 42.6 g (control), 43.6 g (0.63 mg/kg), 46.7 g (1.25 mg/kg) and 41.6 g (2.5 mg/kg). Survival rate incubated pups, 24 hours after delivery was: 81.4% (control), 80.4% (0.63 mg/kg), 97.4% (1.25 mg/kg), and 60.0% (2.5 mg/kg).

Mean litter size was low in all groups, but no statistically significant differences between groups were noted. Also, no differences between groups were seen with regard to number of live, dead and resorbed fetuses, birth weight and 24 hour survival rate. No teratogenic or embryotoxic effects were observed in rabbit fetuses.

E) Oral Male and Female Fertility Study in Wistar Rats

Oral male and female fertility study in Wistar rats (Segment I)

Three hundred and twenty Wistar rats (160 males and 160 females) were used in this experiment. Groups of 20 males and 20 females each received 0, 10, 40 and 160 mg/kg domperidone daily. Males received the drug a minimum of 60 days prior to mating with non-dosed females and females a minimum of 14 days prior to mating with non-dosed males and further throughout gestation. Body weight gain was normal in all dosed and non–dosed females, except for a lower weight gain (due to lower food consumption) in the high-dosed females.

Only two animals died during the study: one low-dosed female and one non–dosed female coupled with a high–dosed male died during the study. There was no difference in gestation between all groups of dosed and non–dosed females. No embryotoxic or teratogenic effect was seen and fertility was not affected in males and females.

F) Oral Embryotoxicity and Teratogenicity Study in Wistar Rats during the peri-and post-natal Period

Oral embryotoxicity and teratogenicity study in Wistar rats during the peri- and post-natal period (Segment III)

Eighty female Wistar rats were divided into four groups of 20 animals each and received 0, 10, 14 and 160 mg/kg domperidone orally from day 16 of gestation through a 3 week lactation period. There was significantly lower body weight gain in the high-dosed females with decreased food consumption. One low-dosed female died during the course of the experiment. Pregnancy rates were 95%, 90%, 70%, and 90% respectively in the control, low, mid and high dose groups. The percentage of live and dead foetuses at birth were respectively: 97.1%, 2.9% (control), 98,4%, 1.6% (low dose), 92.7%, 7.3% (mid dose) and 86.1%, 13.9% (high dose). No abnormalities were noted in any of groups. Pups of all groups showed normal body weight gain during a 3 week neonatal period,. After 3 weeks, at weaning, survival rate of pups born to control dams was 85.5% as compared to 77.2% at 10 mg/kg, 72.1% at 40 mg/kg and 32.3% at 160 mg/kg dosed dams. The effects observed at high dose are probably due to maternal toxicity.

REFERENCES

1. Brodgen RN, ed. Focus on Domperidone and gastroduodenal motility disorders. Drugs 1982; 24:353-400.

2. Hoffbrand BI, ed. Domperidone in the treatment of upper gastrointestinal symptoms. Postgrad Med J 1979; 55 (Suppl. 1).

3. Towse G, ed. Progress with Domperidone, a gastrokinetic and antiemetic agent. Royal Society of Medicine Series; Number 36, 1981.

4. Brouwers JRBJ, Assies J, Wiersinga WM, Huizing G, Tygat GN. Plasma prolactin levels after acute and subchronic oral administration of domperidone and of metoclopramide: a cross-over study in healthy volunteers. Clin Endocrinol 1980; 12:435-440.

5. Laduron PM, Leysen JE. Domperidone, a specific *in vitro* dopamine antagonist, devoid of an *in vivo* central dopaminergic activity. Biochem Pharmacol 1979; 28:2161–2165.

6. Wauquier A, Niemegeers CJE, Janssen PAJ. Neuropharmacological comparison between domperidone and metoclopramide. Japan J Pharmacol 1981; 31:305-314.

7. Niemegeers CJE, Schellekens KHL, Janssen PAJ. The antiemetic effects of domperidone, a novel potent gastrokinetic. Arch Int Pharmacodyn 1980; 244:130-140.

8. Corinaldesi R, Stanghellini V, Zarabini GE et al. The effect of domperidone on the gastric emptying of solid and liquid phases of a mixed meal in patients with dyspepsia. Curr Ther Res 1983; 34:982-986.

9. Heykants J, Knaeps A, Meuldermans W, Michiels M. On the pharmacokinetics of domperidone in animals and man. Eur J Drug Metab Pharmacokin 1981; 6:27-70.

10. Van Ganse W, Van Damme L, Van de Mierop L, Deruyterre M, Lauwers W, Coenegrachts J. Chronic dyspepsia: double-blind treatment with domperidone (R33812) or a placebo. A multicentre therapeutic evaluation. Curr Ther Res 1978; 23:695-701.

11. Agid Y, Quinn N, Pollack P, et al. The treatment of Parkinson's disease with dopaminergic agonists in combination with domperidone. In: Corsini GU, Gessa GL, eds. Apomorphine and other dopaminomimetics, Vol. 2: Clinical Pharmacology, New York: Raven Press, 1981: 107-115.

12. Quinn N, Illas A, Lhermitte F, Agid Y. Bromocriptine and domperidone in the treatment of Parkinson disease. Neurology 1981; 31:662-7.

13. Milo R. Use of the peripheral dopamine antagonist, domperidone, in the management of gastrointestinal symptoms in patients with irritable bowel syndrome. Curr Med Res Opin 1980; 6:577-584.

14. Goethals C. Domperidone in the treatment of postprandial symptoms suggestive of gastroesophageal reflux. Curr Ther Res 1979; 26:874-880.

15. Lienard J, Janssen J, Verhaegen H, Bourgeois E, Willcokx R. Oral domperidone (R33812) in the treatment of chronic dyspepsia: a multicentre evaluation. Curr Ther Res 1978; 23:529-537.

16. Miyoshi A, et al. Investigation of clinical optimum dose of domperidone against unidentified gastrointestinal complaints. Shinryoto Shinyaku 1980; 17:109-119.

17. Product Monograph for Motilium® (domperidone maleate). Date of Revision: March 19, 2001. Janssen-Ortho Inc. Toronto, Ontario.

18. A single dose bioequivalence evaluation of 10 mg domperidone maleate tablets in eighteen healthy volunteers.

19. van Noord C., Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventriciular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf 2010 Nov 1;33(11)1003-14.

20. Johannes CB, Voras-Lorenzo C, McQuay LJ, Midkiff KD, Fife d. Risk of serious ventricular arrythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiology and Drug Safety 2010; 19:881-888.

21. Product Monograph for TEVA-DOMPERIDONE, Control #152087, dated January 23, 2012.

CONSUMER INFORMATION

[Pr]AVA-DOMPERIDONE
Domperidone maleate

This leaflet a part of the "Product Monograph" published when AVA-DOMPERIDONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AVA-DOMPERIDONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AVA-DOMPERIDONE is used to treat symptoms of slowed stomach emptying seen in people with some gastrointestinal disorders (e.g. gastritis- inflammation of the GI tract). AVA-DOMPERIDONE is also used to reduce symptoms such as nausea and vomiting caused by some drugs used to treat Parkinson's disease.

What it does:
AVA-DOMPERIDONE increases the mild digestive contractions of the esophagus and stomach and helps to more effectively coordinate the emptying of food from the stomach into the intestine. It also helps to more effectively move digesting food material through the small intestine.

When it should not be used:
In should not be used in patients who are known to be allergic to ~~it~~ AVA-DOMPERIDONE or any of the nonmedicinal ingredients (See What the nonmedicinal ingredients are). It should not be used in patients who show signs of bleeding in the stomach or intestines, or who may have an obstruction or perforation of the stomach or intestines.

It should not be used in patients who have a tumour associated with the pituitary gland known as a prolactinoma.

What the medicinal ingredient is:
DOMPERIDONE Maleate

What the important nonmedicinal ingredients are:

Cornstarch, croscarmelose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, sodium docusate 85%-sodium benzoate 15% and, titanium dioxide, triacetin.

What dosage forms it comes in:
AVA-DOMPERIDONE is available as 10 mg domperidone tablets (as domperidone maleate).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

AVA-DOMPERIDONE may be associated with an increased risk of heart rhythm disorder and sudden death (cardiac arrest). This risk may be more likely in those over 60 years old or taking doses higher than 30 mg per day. AVA-DOMPERIDONE should be used at the lowest effective dose in adults

BEFORE you use AVA-DOMPERIDONE talk to your doctor or pharmacist if:

- you have, or have ever had breast cancer
- you have an irregular heartbeat, or any other kind of heart disease
- you have any kind of kidney disease
- you are pregnant or plan to become pregnant
- you are breast feeding. AVA-DOMPERIDONE is excreted in breast milk. Discuss with your doctor.
- you experience any kind of unusual discharge of breast milk
- you are a male and have any kind of irregular growth of the breasts
- you are taking a drug called ketoconazole, or a drug called nefazodone
- you are taking any other medications including those available without a prescription and natural health products.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with AVA-DOMPERIDONE include:

- a drug called ketoconazole
- any kind of drug known as:
  - an "anticholinergic" drug
  - an antifungal drug
  - an antibiotic drug
  - a drug to treat AIDS
  - a drug called nefazodone

PROPER USE OF THIS MEDICATION

Usual adult dose:
For disorders involving movement of food through the stomach and intestines: one 10 mg tablet taken 3 to 4 times per day, 15 to 30 minutes before meals, and at bedtime if required. As directed by your doctor, the dose may be increased to 20 mg 3 to 4 times per day.

For nausea and vomiting associated with drugs for Parkinsons

disease: 20 mg taken 3 to 4 times per day.
In all cases, AVA-DOMPERIDONE should only be used at the lowest effective dose.

Overdose:

Symptoms of overdosage may include drowsiness, disorientation, difficulty with normal body movements, irregular heartbeat and lowered blood pressure.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most side effects will gradually disappear with continuing administration of AVA-DOMPERIDONE and are easily tolerated. The more serious or troublesome side effects are dose related and gradually resolve after the dose is lowered or if administration of the drug is discontinued.

Common side effects include dry mouth, headache and migraine. Uncommon side effects include abdominal cramps, diarrhea, regurgitation (bring up stomach contents), nausea and rash. If these side effects become troublesome, talk to your doctor.

Contact your doctor if the more serious or troublesome side effects occur such as galactorrhea (excessive or spontaneous flow of breast milk), gynecomastia (excessive development of male mammary gland) or menstrual irregularities (spotting or delayed periods).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	palpitations		✓	
	irregular heart beat (arrhythmia)			✓
	dizziness			✓
	fainting			✓

This is not a complete list of side effects. For any unexpected effects while takingAVA-DOMPERIDONE, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15-30°C. Protect from light. Unit dose strips should be stored between 15-25°C and protected from high humidity and light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting **Avanstra Inc** at:

Avanstra Inc.
Suite 110
10761-25th street NE
Calgary, AB
T3N 0A4
Telephone: 1-855-708-3678
Facsimile: 1-855-227-5833
www.avanstra.com

Last revised: April 28, 2012