PRODUCT MONOGRAPH

PrFTP-DOMPERIDONE MALEATE 10 mg tablets

12.72 mg as domperidone maleate

Manufacturer Standard

Modifier of upper gastrointestinal motility

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(12.72 mg as domperidone maleate)

Manufacturer Standard

THERAPEUTIC CLASSIFICATION

Modifier of upper gastrointestinal motility

ACTIONS AND CLINICAL PHARMACOLOGY

Domperidone maleate is a peripheral dopamine antagonist structurally related to the butyrophenones with antiemetic and gastroprokinetic properties.

The action of domperidone is defined by an effective increase of esophageal peristalsis and of lower esophageal sphincter pressure (LESP), an increase in gastric motility and peristalsis, an enhancement of gastroduodenal coordination and, as a consequence, to facilitated gastric emptying and decreased small bowel transit time.

The mechanism of action of domperidone is attributed to its peripheral dopamine receptors blocking properties. The antiemetic effect of domperidone was demonstrated by the blockage of emesis induced stimulation of the chemoreceptor trigger zones (situated outside the blood-brain barrier) by apomorphine, hydergine, morphine or levodopa. Indirect evidence exists that emesis is also inhibited at the gastric level, as domperidone inhibits emesis induced by oral levodopa and concentrations localized on the gastric wall following oral administration of domperidone are much greater than the concentrations found in the plasma or other organs. Domperidone was not found to

produce central effects, due to the fact that it does not readily cross the blood-brain barrier.

Domperidone produces an elevation of serum prolactin levels without changes in circulating aldosterone levels.

In man, the absorption of domperidone is defined by a peak plasma level within 10 to 30 minutes following intramuscular injection, and 30 minutes after oral (fasted) administration. Two hours after oral administration, plasma concentrations are lower than after intramuscular injection, indicating the occurrence of hepatic first-pass and gut wall metabolism. Peak plasma concentrations after an i.m. injection of 10 mg are 40 ng/mL, 20 ng/mL after a single 10 mg tablet, and 70-100 ng/mL after an oral dose of 60 mg (tablets or oral drops). The half-life was approximately 7.0 hours for each dosage form. Plasma protein binding as calculated from tritiated domperidone concentrations of 10 and 100 ng/mL, were 91.7% and 93.0%, respectively.

Domperidone's metabolism was characterised by the hydroxylation and oxidative N-dealkylation pathways, resulting in two products: hydroxydomperidone and 2,3-dihydro-2-oxo-1-H-benzimidazol-1-propionic acid. Radiolabelling experiments with oral doses of 40 mg ^{14}C-domperidone in healthy volunteers showed an excretion of 31% of the radioactivity in urine and 66% in faeces over a period of 4 days.

BIOAVAILABILITY

The relative bioavailability of GMD 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
GMD Inc.	210.73	0.91	71.72	223.86
Janssen	217.10	0.83	74.76	231.49

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

INDICATIONS AND CLINICAL USE

Domperidone maleate is indicated for the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis. Domperidone maleate may also be used to prevent gastrointestinal symptoms associated with the utilization of dopamine agonist anti-parkinsonian agents.

CONTRAINDICATIONS

Domperidone maleate is contraindicated in patients with known sensitivity or intolerance to the drug. The use of domperidone should be contraindicated when the situation of gastrointestinal stimulation might be dangerous eg. gastrointestinal haemorrhage, mechanical obstruction.

Domperidone is also contraindicated in patients with a prolactin releasing pituitary tumour (prolactinoma).

WARNINGS

Dopamine receptor blocking agents produce an elevation of prolactin levels which persists during chronic administration. Tissue culture experiments demonstrate that

approximately 1/3 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 having previously been detected as having breast cancer. Although elevated serum prolactin levels were observed with certain disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence, its clinical significance remains unknown for most patients.

An increase in mammary neoplasm has been observed in rodents after chronic administration of dopamine receptor blocking agents. The association of mammary tumorigenesis with chronic administration of these drugs was not demonstrated by either clinical studies or epidemiologic studies. Insufficient data is available to develop a conclusion at this time.

Use in pregnancy:

Although animal studies have not shown drug related teratogenic or primary embryotoxic effects on animal foetuses (see Toxicology section), no comparable studies have been performed in pregnant women. Therefore, domperidone maleate should not be used in pregnant women unless the benefits outweigh the potential hazards to the mother and embryo or foetus.

Use during lactation:

Very low concentrations of domperidone are excreted in breast milk. Caution should be exercised when domperidone is administered to nursing mothers.

Use in children:

Domperidone maleate should not be used for children since its safety and efficacy have not been adequately established in children.

PRECAUTIONS

In patients who develop galactorrhea and/or gynecomastia, withdrawal of the drug will result in the relief of these symptoms.

Drug Interactions:

The beneficial effects of domperidone maleate may be compromised by the concomitant use of anticholinergic drugs.

Since domperidone produces an increase of gastric and small intestinal motility, absorption of the drug may be accelerated in the small intestine, while absorption of the drug through the stomach is slower.

Domperidone should be carefully administered in combination with MAO inhibitors.

Domperidone maleate absorption was not decreased when taken in combination with antacids or H_2-receptor blockers.

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.

ADVERSE REACTIONS

In clinical studies, the overall incidence of side effects after oral administration was <7% of which some were an extension of the dopamine antagonist properties of domperidone. Most side effects resolve spontaneously during continued therapy or are easily tolerated.

The most serious or troublesome side effects are galactorrhea, gynecomstia and menstrual irregularities. These side effects are dose-related and are gradually resolved after reduction of dosage or discontinuation of therapy.

Central nervous system (4.6%):
Dry mouth (1.9%), headache/migraine (1.2%), insomnia, nervousness, dizziness, thirst, lethargy, irritability (all <1%).

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

Endocrinological (1.3%):
Hot flushes, mastalgia, galactorrhea, gynecomastia, menstrual irregularities.

Mucocutaneous (1.1%):
Rash, pruritus, urticaria, stomatitis, conjunctivitis.

Urinary tract (0.8%):
Urinary frequency, dysuria.

Cardiovascular system (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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No incidence of domperidone maleate overdosage has been reported. However, based on the pharmacological properties of domperidone, central nervous system (drowsiness, disorientation and extrapyramidal reactions, especially in children) and cardiovascular (arrhytmias, hypotension) effects might possibly occur. Symptoms are self-limiting and usually disappear within 24 hours.

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 administration 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

Upper gastrointestinal motility disorders:

In adults, the usual dosage is 10 mg orally 3 to 4 times daily, 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 daily.

Nausea and vomiting associated with dopamine agonist antiparkinsonian agents:

In adults, the usual dosage is 20 mg orally 3 to 4 times daily. Higher doses may be required to achieve symptom control while titration of the anti-parkinsonian medication is occurring.

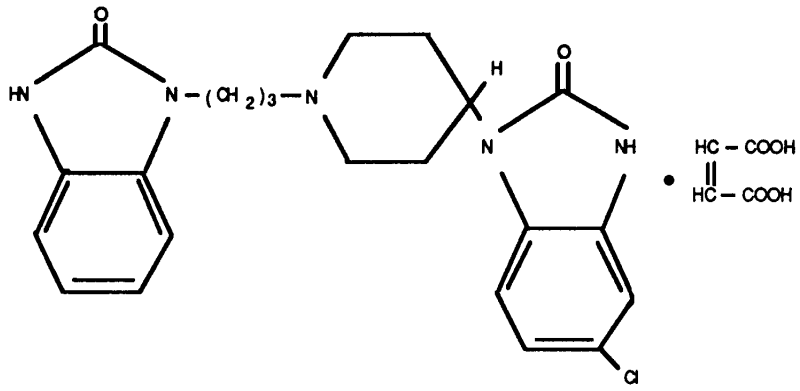
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper or common 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-2 H- benzimidazol-2-one (z)-2-butenedioate (1:1)

Structural formula:



Molecular formula: $C_{22}H_{24}N_5O_2Cl \bullet C_4H_4O_4$

Molecular weight: 541.99

Description

Physical form: White to off white crystalline powder.

Solubility:

in water:	0.10%
In ethanol:	0.1%
In PEG 400:	0.5%
In PPG:	1.3%
In CHCl3	0.004%

pka value: pka = 7.890

Partition coefficient: log P= 3.90 at pH 10.2

Melting range: 225 to 231°C·

Composition: **Each white to faintly cream film-coated tablet contains:** domperidone maleate 12.72 mg (equivalent to domperidone 10 mg), lactose and cornstarch, microcrystalline cellulose, povidone, magnesium stearate, sodium docusate 85%-sodium benzoate 15% and croscarmelose sodium, polyethylene glycol, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sorbitol, titanium dioxide.

Stability and Storage Recommendations Store at room temperature between 15 and 30˚C. Protect from light and moisture.

AVAILABILITY OF DOSAGE FORMS

FTP-DOMPERIDONE MALEATE is a round, plain-coated, biconvex white tablet, engraved "K113" on one side and plain on the other side. Available in HDPE bottles containing 500 tablets.

PHARMACOLOGY

Domperidone is a dopamine antagonist which does not readily cross the blood-brain barrier and exerts its primary effect on peripheral dopamine receptors.

In vitro, ^{3}H-domperidone binds specifically and selectively the striatal dopamine receptors in mice and rats. *In vivo*, no displacement of ^{3}H-piperone in rat brain dopaminergic areas and no increase in rat brain homovanillic acid (HVA) concentrations were observed. In addition, domperidone at doses up to 100 times in excess of the anti-emetic dose produced no changes in behaviour, conditioned reflexes, intracranial self-stimulation or EEG tracings. These studies indicate that domperidone does not cross the blood-brain barrier.

Intravenous doses of domperidone given in dogs and baboons, produced a dose-dependent increase of the resting tone of the lower esophageal sphincter. Gastric relaxation induced by apomorphine was completely blocked by injecting 1 mg/kg i.v. domperidone in anaesthetized dogs.

In the isolated gastroduodenal preparation of the guinea pig, domperidone antagonized dopamine's antroduodenal coordination but not the antroduodenal coordination effect of noradrenaline.

In dogs, 0.35 mg/kg and 0.7 mg/kg i.v. domperidone significantly increased the distension of the pyloric sphincter without affecting the frequency of the pyloric relaxation.

In beagle dogs, intravenous doses of 200 or 1 000 μg/kg domperidone produced a significant increase in the contractile activity in the antrum, without changing the mean blood pressure.

In dogs, domperidone produced no changes on the emptying pattern of semi-solid, but significantly reduced the stationary phase of a solid meal by 50%. Emptying rate of solids was unchanged.

In dogs, the apomorphine-induced emesis (s.c. injection of 0.31 mg/kg) was completely inhibited by domperidone. ED_{50} s.c. was 0.007 mg/kg, 0.031 mg/kg orally, and 0.10 mg/kg rectally.

In addition, domperidone was very effective against emesis induced by hydergine, levodopa and morphine, but it was ineffective against copper sulphate-induced emesis.

In rats, domperidone significantly increased plasma prolactin release, which was more pronounced (4-fold) in female rats than in male rats.

In Rhesus monkeys, domperidone also induced a marked increase in plasma prolactin concentration without changes in plasma 18-hydroxycortisone and aldosterone.

TOXICOLOGY

Acute Toxicity

Route	Animals	Number of Animals	LD_{50} mg/kg 7 days
I.V.	Mice	40 M 30 F	56.5 (43.1 - 73.8) 56.8 (43.5 - 74.2)
	Rats	50M 30 F	56.3 (43.1 - 73.6) 68.8 (52.5 - 89.9)
	Guinea-pigs	30 M 30 F	42.9 (32.8 - 56.1) 44.4 (34.0 - 58.0)
	Dogs	33 M & F	42.7 (32.7 - 55.9)
P.0.	Mice	30 M 30 F	> 1280 > 1280
	Rats	60 M 20 F	> 1280 > 1280
	Guinea-pigs	30 M 30 F	796 (424-1493) > 1280
	Dogs	6 M & F	> 160
S.C.	Dogs	6 M & F	> 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

Route:	i.v.
Species:	Wistar rats
# of animals:	10 M & 10 F/group
Dose administered:	0, 2.5, 10 or 40 mg/kg once daily, six days a week.
	Duration: 3 weeks

Results:

No effect on mortality, behavior and appearance.

At 40 mg/kg:

Significant reduction of food consumption and body weight in males. Increase of segmented heterophils and decrease of lymphocytes. Increase in alkaline phosphatase in females (at all dosages), and increase of heptoglobin in both sexes.

Moderate to strong irritation of the tail with progressive necrosis. Stimulation of the mammary glands in several females. Decrease in spleen weight, decrease in the weight of most organs (especially in males).

Histopathology examination reveals reduction of number of corpora lutea in the ovary, reduction of oesinophilic infiltration of the uterine wall and more folded uterine mucosa, mucification of the vagina, female aspect of mammary glands in males, and glandular development with secretion in females, more extended chromophobe tissue of the hypophysis (in all dosages).

Subacute Toxicity (cont'd)

Route:	i.v.
Species:	Beagle dogs
# of animals:	3 M & 3 F/group
Dose administered:	0, 1.25, 5 or 20 mg/kg once a day, six days a week. Duration: 3 weeks
Results:	No effect on mortality.

At 20 mg/kg:

Emesis and reduced appetite were observed. Marginal decrease in haematocrit and haemoglobin were observed. Heart rate, ECG, blood pressure, serum analysis and urinalysis remained normal. Slight increase in relative liver weight and slight decrease in absolute and relative adrenal weight. Histopathology examinations showed a reduction and absence of germatogenisis, atrophy of the prostate, degranulation of the hythrosinophilic cells of the hypophysis.

Route:	p.o.
Species:	Wistar rats
# of animals:	10 M & 10 F/group
Dose administered:	0, 10, 40 or 160 mg/kg. Duration: 15 weeks

Results:

At 160 mg/kg:

Decrease in appetite and weight gain. Two deaths were noted unrelated to drug administration. Hematology, serum analysis and urinalysis were normal except for a decrease in creatinine. Stimulation of the mammary glands was noted (in all cases) Histopathology examination showed a mucification of the vaginal epithalium, reduction in number of corpora luted (in all doses), female aspect with secretions in males, marked development of glandular tissue with secretions in females (at all doses).

Subacute Toxicity (cont'd)

Route: p.o.

Species: Beagle dogs

# of animals: 3 M & 3 F/group

Dose administered: 0, 2.5, 10 or 40 mg/kg. Duration: 15 weeks

Results:

At 40 mg/kg:

Decrease in appetite, ocular discharge and ptosis. Decreased food consumption and persistent body weight loss were observed. Heart rate, ECG, and blood pressure were normal. Haematological parameters were normal except for a decrease in haematocrit, haemoglobin and red blood cells. Relative liver weight increase in dose-related. Histopathological examination revealed desquamation and some degeneration of germinal epithelium with absence of spleenatogenesis in 75% of males, prostatic atrophy (also at 10 mg/kg), thymus involution in 75% of females. More extended erythrosinophilic tissue in the hypophysis in males and females (at mid-dose also).

Chronic Toxicity

Route: p.o.

Species: Wistar rats

# of animals: 40 M & 40 F/group

Dose administered: 0, 10, or 160 mg/kg daily, seven days a week. Duration: 6-12-18 months.

Results:

No dose-related mortality was observed in 6, 12 and 18 months. Increased appetite with 10 and 40 mg/kg in females especially after 12 and 18 months.

Stimulation of mammary glands in females at all doses and in males at 160 mg/kg after 18 months.

Decreased food consumption at 160 mg/kg in both sexes after 6 months and in males only after 12 and 18 months.

Hematology and biochemistry evaluations revealed: slight increase of non-pigmented heterophiles in females with 40 and 160 mg/kg after 12 months, marginal increase of monocytes in females with 40 and 160 mg/kg after 18 months and marginal increase of monocytes in females with 40 and 160 mg/kg after 12 months.

Necropsy examinations in dosed as well as non-dosed animals revealed pneumonia, lung abcesses, alopecia, thymus involution.

Stimulation of mammary glands in females at all doses at 6, 12 and 18 months, and in males with 160 mg/kg after 18 months.

Histopathological examinations revealed:

- enhanced prostatins at all doses except with 10 mg/kg after 6 months.
- progestational aspect of female genital tract at all doses after 6 and 12 months.
- female aspect or atrophy of mammary gland in males at all doses.
- stimulation of mammary glands in females at all doses after 6 and 12 months and at 160 kg/mg after 6 and 18 months.
- inverted or irregular gradient of adrenal fat in males at 160 mg/kg after 6, 12 and 18 months and in females at 40 mg/kg after 6 and 12 months. Absence of fat gradient in females at 160 kg/mg after 6 months.
- chronic stimulations of the chromophobe or erythrosinophilic tissues of the hypophylis at all doses.

Chronic Toxicity (cont'd)

Route: p.o.

Species: Beagle dogs

# of animals: 12 M & 12 F

Dose administered: 0, 2.5, 10, or 40 mg/kg daily, seven days a week. Duration: 12 months.

Results:

One death was observed at 8 weeks of 40 mg/kg domperidone due to gastroenteritis and peritonitis (not drug-related). No behaviour and appearance abnormalities were drug-related.

At 40 mg/kg:

Decreased food consumption causing a lower terminal body weight. ECG, heart rate and blood pressure were normal. Slight decrease of haemotocrit, haemoglobin and red blood cells (also at 10 mg/kg), and slight increase in monocytes and thrombocytes. Marginal to moderate increase of haptoglobin (also 10 mg/kg). Increase of relative liver weight.

Hispathological examinations revealed changes in testis (degeneration with impairment of spermatogenesis), prostate (atrophy and/or fibrosis) and eyes (keratitis).

Carcinogenicity Toxicity

Route:	p.o.
Species:	Albino Swiss mice
# of animals:	200 M & 200 F
Dose administered:	0, 2.5, 10, or 40 mg/kg body/weight/day. Duration: 8 months.

Results:

No dose-related effects on health, behaviour, appearance, overall survival rate or gross pathology were observed.

Histopathological examinations revealed no difference on number of tumor-bearing mice were observed between groups. Increase in mammary carcinomas was significantly observed with 40 mg/kg in females.

No dose-related effects on health, behaviour, appearance, survival rate or gross pathology were seen.

Histopathological examination revealed no difference on total incidence of tumor-bearing rats between groups. At 40 mg/kg, marginal increase of incidence of pituitary adenomas in males, and slight tendency towards an increase in mammary carcinomas in females were noted. High number of thyroid adenomas was observed in the mid-dosed females which was not so with those dosed at 40 mg/kg.

Mutagenicity studies:

No evidence of any mutagenic potential of domperidone was noted *in vitro*, chromosomal aberrations in human lymphocytes, in micronucleus test in mice and in rats, chromosomal aberrations in liver enzyme rats, in dominant lethal test in male and female germ cells, and in sex-linked recessive lethal test on drosophila.

REPRODUCTION AND TERATOGENICITY STUDIES

Intravenous embryotoxicity and teratogenicity study in Wistar rats

No. of animals	Dose administered	Results
80 F	0, 2.5, 10 and 40 mg/kg day from day 6 to day 15 of gestation	No mortality was noted. **Dosage** **0 2.5 10 40** Pregnancy rates % 95 100 95 85 % live 97.2 94.8 92.1 90.5 % dead 0 0 0 0 % resorbed foetuses 2.8 5.2 7.9 9.5 Slight increase in resorptions with increasing dosages was observed. No difference of abnormalities were noted between dosage groups.

Oral embryotoxicity/teratogenicity in rats (Segment II)

No. of animals	Dose administered	Results
80 F	0, 10, 40 or 160 mg/ kg daily from day 6 to day 15 of gestation	Pregnancy rate % / Dosage (mg/kg): 65 / 160; 100 / 10; 90 / 0. No effect was observed on number of implantations, pregnancies and pups, litter size and weight at birth, number of resorptions, live and dead foetuses, number and distribution of live, dead and resorbed embryos. No embryo-toxicity or teratogenicity were observed.
80 F	0, 5, 20 or 80 mg/kg daily from day 6 to day 15 of gestation	Pregnancy rate % / Dosage (mg/kg): 95 / 0; 80 / 5; 100 / 20; 95 / 80. No embryotoxicity or teratogenicity were observed.

Oral embryotoxicity/teratogenicity in rats (Segment II) (cont'd)

No. of animals	Dose administered	Results
80 F groups of 20	0, 160, 320 or 640 mg/kg daily from day 6 to 15 of gestation	Three females died: one at 320 and 2 at 640 mg/kg. Causality of death was not established.
		Pregnancy rate % / Dosage (mg/kg) 95 / 0 85 / 160 20 / 320 25 / 640
		Resorptions increased with dose and was 100% with 640 mg/kg. Decrease of litter size and pup weight at delivery were observed at 160 and 320 mg/kg. No teratogenicity drug related was noted, but maternal toxicity was observed at 640 mg/kg.

Oral three generation reproduction study in Wistar rats.

No. of animals	Dose administered	Results
40 M 120 F	0, 10, 40 or 160 mg/100 g food, from day 0 of mating and further through breeding and weaning	Significant lower body weight was observed in the first generation at 160 mg/100g (correlated with decreased of food consumption). No mortality and pregnancy rates differences were observed between groups. Decrease in litter size and number of live foetuses were observed at 160 mg/100 g in second generation which was attributed to maternal toxicity. No differences in abnorma-lities were observed between treated and untreated groups.

Intravenous embryotoxicity and teratogenicity study in the New Zealand white rabbit.

No. of animals	Dose administered	Results
60 F group of 20	0, 0.63, 1.25 mg/kg/day from day 6 to day 18 of gestation	**Dosage** **0 0.63 1.25** Survival rate % 100 85 100 Pregnancy rate 100 85 90 % live 90.2 99.2 97.1 % dead 0 0 0 % resorbed foetuses 2.9 0.8 2.9 average birthweight of live pups(g) 34.6 35.3 36.9 24 hr. survival rate of incubated pups 77.7 76.7 76.5 Three animals died at 0.63 mk/kg. No changes were observed in body weight gains. No embryotoxic or teratogenic effects were observed with domperidone.

Intravenous embryotoxicity and teratogenicity study in New Zealand white rabbit (Segment II)

Route: I.V.

Species: New Zealand white rabbit

# of animals: 60 in groups of 15

Dose administered: 0, 0.63, 1.25 and 2.5 mg/kg from day 6 to day 8 of gestation.

Results: Mortality was observed in 3/15 with no drug, 1/15 at 0.63 mg/kg, 2/15 at 1.25 mg/kg and 8/15 at 2.5 mg/kg.

No pregnancy rates differences were observed between groups.

	Dosage			
	0	**0.63**	**1.25**	**2.5**
Average size litter	4.9	3.9	3.9	1.7
% live	4.3	3.8	3.8	1.7
% dead	0.6	0.1	0.1	0
% resorbed foetuses	1.7	0.3	1.7	2.5
At resection average birthweight of live pups (g)	42	43.6	46.7	41.6
24 hr. survival rate of incubated pups	81.4	80.4	97.4	60

No differences between groups were observed on number of live, dead and resorbed foetuses, birthweight and 24 hour survival rate.

No teratogenic or embryotoxic effects were observed in rabbit foetuses.

Oral embryotoxicity and teratogenicity studies in New Zealand white rabbit.

Route: Oral
Species: New Zealand white rabbit
# of animals: 60 F in groups of 20
Dose administered: 0, 10 or 40 mg/kg from day 6 to day 18 of gestation.

Results:

Mortality was noted at 10 mg/kg (1/20) and 40 mg/kg (9/20). The causality of death was lobular pneumonia in 2 cases, enteritis in one case, and pneumonia with mucoid enteritis in another case.

	Dosage		
	0	**10**	**40**
Rate of pregnancies (%)	85	85	85
Average litter size	6.2	5.7	5.5
% live	83	72.6	76.6
% dead	2.6	1.6	2.6
% resorbed foetuses	15.3	25.8	20.8
At resection average birthweight of live pups (g)	41.5	40.7	36.3
24 hr. survival rate of incubated pups	75	61.1	40.7

No abnormalities were observed in any group.

Conclusion:

Domperidone did not produce teratogenic effects at doses of 10 and 40 mg/kg. However, a slight increase in resorptions in dosed animals with evidence of maternal toxicity was observed.

Oral embryotoxicity and teratogenicity studies in New Zealand white rabbits.

No. of animals	Dose administered	Results
60 F	0, 5, 20 mg/kg/day by gavage from day 6 to day 18 of gestation	Mortality was observed at 5 mg/kg (3/20) and at 20 mg/kg (12/20).

	Dosage		
	0	**5**	**20**
Pregnancy rate (%)	60	70	40
% live	70	64.6	82.4
% dead	0	0	5.9
% resorbed foetuses	30	35.4	11.7
at resection average birthweight of live pups (g)	42.5	39.0	34.7
24 hr. survival rate of incubated pups	54.3	52.4	14.3

Conclusion: No teratogenic effect was noted. Maternal toxicity was observed at 5 and 20 mg/kg as pregnancy rate decreased (at 20 mg/kg), mortality rate and weight gain decreased (at 5 and 20 m/kg).

Oral fertility in Wistar rats

No. of animals	Dose administered	Results
160 M/160 F in groups of 20	0, 10, 40 and 160 mg/kg/day male: minimum of 60 days prior to mating with untreated female. female: minimum of 14 days prior to mating with untreated male	Body weight gain was normal in all groups except for a lower gain (due to lower food consumption) at 160 mg/kg/day in females. Mortality was noted in low dosed females (1/20) and in control group where one female was coupled with 160 mg/kg male. No difference was observed on gestation. No embryotoxic or teratogenic effect was noted and fertility was not affected in both sexes dosed with domperidone.

Oral embryotoxicity and teratogenicity study in Wistar rats during pre- and post-natal periods (Segment III)

No. of animals	Dose administered	Results
80 F in groups of 20	0, 10, 40 and 160 mg/kg/day from day 16 of gestation through a 3 week lactation period	Significant lower body weight gain with decreased of food consumption was observed with 160 mg/kg. Mortality was observed in one female at 10 mg/kg/day. **Dosage** **0 10 40 160** Pregnancy rate (%) 95 90 70 90 % live 97.1 98.4 92.7 86.1 % dead foetuses 2.9 1.6 7.3 13.9 3 weeks survival rate of born pups 85.5 77.2 72.1 32.3 Effects observed at 160 mg/kg/day are probably due to maternal toxicity.

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