PRODUCT MONOGRAPH

PrMOTILIUM* TABLETS

(domperidone maleate)

Modifier of Upper Gastrointestinal Motility

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PRODUCT MONOGRAPH

PrMOTILIUM*

domperidone maleate tablets

THERAPEUTIC CLASSIFICATION

Modifier of Upper Gastrointestinal Motility

ACTIONS AND CLINICAL PHARMACOLOGY

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

Domperidone effectively increases oesophageal peristalsis and lower oesophageal sphincter pressure (LESP), increases gastric motility and peristalsis, enhances gastroduodenal 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 man, 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 70-100 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 91.7 and 93.0%, respectively.

The major metabolic pathways for domperidone in man 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. 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 faeces over a period of 4 days.

INDICATIONS AND CLINICAL USE

MOTILIUM (domperidone maleate) is indicated in the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis. MOTILIUM may also be used to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents.

CONTRAINDICATIONS

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

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

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

WARNINGS

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 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.

Use in Pregnancy

While animal studies have not shown drug related teratogenic or primary embryotoxic effects on animal fetuses (see section on Toxicology), comparable studies have not been performed in pregnant women. For this reason, MOTILIUM (domperidone maleate) should not be used in pregnant women unless the benefit outweighs the potential hazard.

Use during Lactation

Domperidone is excreted in breast milk in very low concentrations. Therefore nursing is not recommended for mothers taking MOTILIUM unless the expected benefits outweigh any potential risk.

Use in Children

The safety and efficacy of MOTILIUM (domperidone maleate) in children has not been established, therefore, domperidone maleate 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

The concomitant administration of anticholinergic drugs may compromise the beneficial effects of MOTILIUM (domperidone maleate).

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.

ADVERSE REACTIONS

In clinical studies with oral MOTILIUM the overall incidence of side effects with domperidone 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 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, 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: (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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Based on the pharmacological properties of domperidone, symptoms of overdosage may include CNS effects (such as drowsiness, disorientation and extrapyramidal reactions, especially in children) and cardiovascular effects (arrhythmia, 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 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:

The usual dosage in adults is 10 mg orally 3 to 4 times a days, 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.

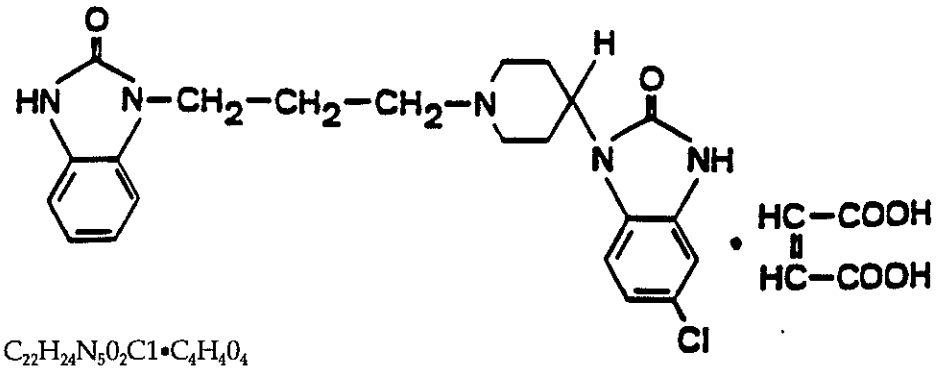
PHARMACEUTICAL INFORMATION

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)

Chemical Structure:



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

Molecular Weight: 425.92 + 116.07 = 541.99

Description: Domperidone maleate is a white to slightly beige coloured powder sparingly soluble in N, N-dimethylformamide and propylene glycol; slightly soluble in water, methanol, and ethanol; very slightly soluble in tetrahydrofuran and insoluble in chloroform.

Composition: Each tablet of MOTILIUM (domperidone maleate) contains 12.72 mg domperidone maleate equivalent to 10 mg domperidone and as non-medicinal ingredients: lactose, corn starch, microcrystalline cellulose, pregelatinized starch, povidone, magnesium stearate, silicon dioxide, polysorbate, hydroxypropyl methylcellulose, and propylene glycol.

Stability and Storage Recommendations: MOTILIUM tablets should be stored at room temperature (15 - 30 °C), protected from light and moisture.

AVAILABILITY OF DOSAGE FORM

MOTILIUM* (domperidone maleate) is available as white to faintly cream, film-coated tablets containing 10 mg domperidone, in HDPE bottles containing 500 tablets. Domperidone is a Schedule F drug.

PHARMACOLOGY

MOTILIUM (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 binds specifically and selectively to mouse and rat striatal dopamine receptors in vitro, domperidone, administered in vivo, 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 dog, domperidone, given intravenously, produced a dose-dependent increase in lower oesophageal 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 the 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 distention 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} was 0.007 mg/kg s.c. and 0.031 mg/kg p.o. for domperidone. 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

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	50 M 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.O.	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:

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 dosed animals. Serum analyses 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 haematocrit and haemoglobin. 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 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 at 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/group) 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 analyses 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 the 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 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 glandular 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 the high dose, and there was a persistent body weight loss. Heart rate, ECG, and blood pressure remained normal in all groups. Haematological parameters were normal except for a decrease in haematocrit, haemoglobin 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 germinal 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 month 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 the 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). Haematology 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 increase of inorganic phosphorus in dosed females (12 months). Urinalysis was normal. Most of the necropsy findings occurring in dosed as well as non-dosed animals were related to the 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 gland 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 in the females 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 doses 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. Haematological values remained normal except for a slight decrease of haematocrit, haemoglobin and red blood cells at 10 and 40 mg/kg and a 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 mg/kg 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: 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 ones.

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 in four groups of 50 males and 50 females. Each group received orally through the drinking water for 18 months, 0.625 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, behaviour or appearance. No dose-related effects on gross pathology were seen.

Histopathological examinations revealed no difference between groups with regard to the number of tumour-bearing mice. The incidences of the various tumour-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 in 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 body 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 adverse effects on survival rate were noticed and no dose-related effects on health, behaviour or 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 tumour-bearing rats when the various dosage groups of the males and females were compared. The incidence of the various tumour 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 tumorigenesis were expected for a dopamine-antagonist given 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 EMBYROTOXICITY/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 foetuses, number and 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 foetuses, 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 group. 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 evidence of maternal toxicity.

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 was also following during a second and third generation as follows: all pups of the F_1 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 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 foetuses 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 in 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 foetuses 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 EMBRYOTOXICITY AND TERATOGENICITY STUDIES IN THE RABBIT

Oral embryotoxicity and teratogenicity study in New Zealand white rabbits

Sixty female New Zealand white rabbits were divided in three groups of 20 animals each and received 0, 10 and 40 mg/kg/day domperidone by gavage from day 6 through day 18 of gestation. There was one death at low dose and 9 deaths at high dose. The cause of death was lobular pneumonia in 2 cases, enteritis in one case and pneumonia with mucoid enteritis is 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 percentages of live, dead and resorbed foetuses 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 was 41.5 g (control), 40.7g (low dose) and 36.3 g (high dose). The 24 hour survival rate of incubated pups was 75% in control,

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 in 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 incubated pups, 24 hours after delivery was: 54.3% (control), 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 white rabbits were divided in 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, 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 foetuses for all groups were respectively 90.2%, 0% and 9.8% for the control, 99.2%, 0% and 0.8% in the low dose group at 97.1%, 0% and 2.9% in the high dose group. The average birth weight of live pups was: 34.6 g (control), 35.3 g (low dose) and 36.9 g (high dose). Survival rate of incubated pups 24 hours after delivery was: 77.7% (control), 76.7% (low dose) and 76.5% (high dose). Domperidone administered under these conditions did not produce any embryotoxic or teratogenic effects.

Intravenous embyrotoxicity and teratogenicity study in New Zealand white rabbits (Segment II)

Sixty female New Zealand white rabbits were divided in 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 3/15 deaths in the control group, 1/15 in the low dose group, 2/15 in the mid dose group, and 8/15 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 the 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 foetuses per female for all groups were respectively: 4.3, 0.6, 1.7 (control), 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 of 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 foetuses, birth weight and 24 hour survival rate. No teratogenic or embryotoxic effects were seen in rabbit foetuses.

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. 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 in four groups of 20 animals each and received 0, 10, 40 and 160 mg/kg domperidone orally from day 16 of gestation through a 3 week lactation period. There was a significant lower body weight gain in 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 the 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 40.0 mg/kg and 32.3% at 160 mg/kg dosed dams. The effects observed at the high dose are probably due to maternal toxicity.

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