PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of Pharmacological, Pharmacokinetics and Toxicity data of Domeperidone have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

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

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Domperidone Maleate is a white to slightly beige coloured powder. Very slightly soluble in water, sparingly soluble in dimethylformamide, slightly soluble in methanol, very slightly soluble in alcohol.

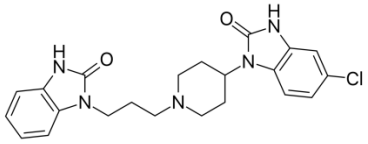
IUPAC name: 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1- yl)propyl]piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one hydrogen (Z)-butenedioate.

Chemical Abstract Services (CAS) Registry Number:

Molecular Weight: 541.99 g/mol

Chemical Formula: $C_{22}H_{24}N_5O_2Cl \bullet C_4H_4O_4$

Molecular Structure:



4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
TOXICITY	**YES**	**NO**	**UNKNOWN**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmental Toxicant	-	√	-
Highly Sensitizing potential	-	√	-

PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

SUMMARY OF HAZARD IDENTIFICATION:

Pharmacodynamics data

Domperidone is a peripherally selective dopamine D_2 and D_3 receptor antagonist. It has no clinically significant interaction with the D_1 receptor, unlike metoclopramide. The medication provides relief from nausea by blocking D receptors. It blocks dopamine receptors in the anterior pituitary gland increasing release of prolactin which in turn increases lactation. Domperidone may be more useful in some patients and cause harm in others by way of the genetics of the person, such as polymorphisms in the drug transporter gene ABCB1 (which encodes P-glycoprotein), the voltage-gated potassium channel KCNH2 gene (hERG/K_v11.1), and the α_{1D}—adrenoceptor ADRA1D gene.

Pharmacokinetics

With oral administration, Domperidone is extensively metabolized in the liver (almost exclusively by CYP3A4/5, though minor contributions by CYP1A2, CYP2D6 and CYP2C8 have also been reported) and in the intestines. Due to the marked first-pass effect via this route, the oral bioavailability of Domperidone is low (13–17%); conversely, its bioavailability is high via intramuscular injection (90%). The terminal half-life of Domperidone is 7.5 hours in healthy individuals, but can be prolonged to 20 hours in people with severe renal dysfunction. All of the metabolites of Domperidone are inactive as D_2 receptor ligands. The drug is a substrate for the P-glycoprotein (ABCB1) transporter and animal studies suggest that this is the reason for the low central nervous system penetration of Domperidone.

Acute Toxicity

Species	Gender	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)
Rat	**M**	**i.v.**	56.3 (43.1-73.6)
	F	**i.v.**	68.8 (52.6-89.9)
Guinea Pig	**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
Rat	**M**	**p.o.**	>1280
	F	**p.o.**	>1280
Guinea Pig	**M**	**p.o.**	796 (424-1493)
	F	**p.o.**	>1280
Dogs	**M & F**	**p.o.**	>160
Dogs	**M & F**	**s.c**	>160

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.

PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

SUMMARY OF HAZARD IDENTIFICATION:	
	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.
Repeated Dose Toxicity (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.

PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

SUMMARY OF HAZARD IDENTIFICATION:	
	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	**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 body weight/day), 10 mg /100 g food/day (10 mg/kg body weight/day) and 40 mg/100 g food/ day

PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

SUMMARY OF HAZARD IDENTIFICATION:	
	(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.
In vivo/In vitro Genotoxicity Studies	**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*.
Reproductive/Developmental Toxicity	**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%

SUMMARY OF HAZARD IDENTIFICATION:	
	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 toxicity.** ***Oral three generation reproduction study in Wistar rats*** Forty young and healthy adult males and one hundred and twenty young and healthy virgin females (Wistar rats) were used as the F0 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 F0 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 2½ months growing period, a second generation was bred from the F1 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 F2 litter were weighed on days 1, 4, 14 and 21. After weaning at day 21 and a further 2½ months growing period, a third generation was bred from the F2 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 F3 pups were weighed. The males and females of the second (F1) and third (F2) generations were dosed continuously at the same dose levels as the F0 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

SUMMARY OF HAZARD IDENTIFICATION:	
	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**

PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

SUMMARY OF HAZARD IDENTIFICATION:	
	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

PERMITTED DAILY EXPOSURE FOR DOMPERIDONE

SUMMARY OF HAZARD IDENTIFICATION:	
	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.
Highly Sensitizing Potential	Domperidone does not comes under highly sensitive material.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	One 10 mg tablet three times per day with a maximum dose of 30 mg per day is recommended for all indications as the risk of serious cardiac events may be increased in association with daily doses > 30 mg.

Clinical therapeutic and adverse effects	For oral dosage form (tablets):
	• Treatment of gastrointestinal motility disorders:
	  ○ Adults—10 milligrams (mg) three to four times daily. Some patients may require higher doses up to 20 mg three or four times daily.
	• Nausea and vomiting:
	  ○ Adults—20 milligrams (mg) three to four times daily.
	
	Headache, dizziness, dry mouth, nervousness, flushing, or irritability may occur the first several days as your body adjusts to the medication. Trouble sleeping, stomach cramps, hot flashes and leg cramps have also been reported.

NOAEL/LOAEL	1.6 mg/kg/day is considered as NOAEL value for Domperidone.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	5	For extrapolation from rats to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.

F3: Duration of Toxicity (Repeat Dose Toxicity)	1	1 year duration study in rodent.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected (Maximum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{1.6 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$ = 0.32 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Domperidone.
- https://www.medicinenet.com/domperidone-oral/article.htm
- https://pdf.hres.ca/dpd_pm/00029629.PDF
- https://chem.nlm.nih.gov/chemidplus/rn/57808-66-9
- https://www.mayoclinic.org/drugs-supplements/domperidone-oral-route/proper-use/drg-20063481