2.6.6.10 Tables and Figures

Table 38. Overview of prasugrel single dose toxicity in mice, rat and dog

Species Strain	Route	Test article Doses[a] (mg/kg)	Sex #/Group	Obs Maximum Nonlethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings
Mice RFVL	Oral[b]	Prasugrel, 2000	10 M, 10 F	2000	>2000	Yellow-brown urine Necropsy: no gross changes
Rat Fischer 344	Oral[b]	Prasugrel, 1000 and 2000	5 M, 5 F	2000	>2000	≥1000 mg/kg: yellow-brown urine and mydriasis 2000 mg/kg: F only; irregular respiration, ↓ locomotor activity, staggering gait, ptosis, and lacrimation; M, F: slight ↓ body weight gain on Day 3 Necropsy: no gross changes
Rat Fischer 344	Oral[b]	Prasugrel or Prasugrel HCl; 0, 500, 1000, and 2000	5 M, 5 F	Prasugrel: 2000 Prasugrel HCl: 1000	Prasugrel: >2000 Prasugrel HCl: 1000 to 2000	<u>Prasugrel HCl and Prasugrel:</u> ≥500 mg/kg: fluorescent yellow urine, no gross pathology ≥1000 mg/kg: ↓ body weight gain <u>Prasugrel HCl:</u> 2000 mg/kg: 3/5 M, 4/5 F died, mydriasis, ↓ spontaneous movement <u>Prasugrel:</u> ≥1000 mg/kg: mydriasis, ↓ spontaneous movement
Dog Beagle	Oral[c]	Prasugrel, 10, 30, 100, 300, 1000, and 2000[d]	1 M, 1 F	2000	>2000	≥30 mg/kg: ↓ platelet aggregation ≥300 mg/kg: emesis 2000 mg/kg: ↑ alkaline phosphatase Histology: hepatocellular atrophy, ground-glass appearance of hepatocellular cytoplasm at 2000 mg/kg

= number, ↓ = decreased, ↑ = increased, [a] single doses, [b] Vehicle = tragacanth 0.5%,
[c] vehicle = none (test article administered as dry material in capsule)

Table 39. Overview of prasugrel repeat-dose toxicity study in mice, rat and dog

Species Strain	Route	Duration of Dosing	Doses (mg/kg)	Sex #/Group	Noteworthy Findings
Mouse B6C3F1	Oral[a]	2 weeks	0, 300, 1000, 2000	10 M, 10 F	≥300 mg/kg: fluorescent yellow urine, ↑ liver weight, hypertrophy of centrilobular hepatocytes ≥1000 mg/kg: ↓ body weight gain, ↓ red blood parameters, ↑ creatinine, single cell necrosis/focal necrosis of hepatocytes 2000 mg/kg: mortality (4 of 10 males), ↑ AST and ALT
Rat Fischer 344	Oral[a]	2 weeks	0, 30, 100, 300, 1000	10 M, 10 F	≥30 mg/kg: brown urine, ↑ platelets (M) ≥100 mg/kg: mydriasis (F), ↑ APTT (M), induction of drug metabolizing enzymes, ↑ liver weight, hypertrophy and acidophilic cytoplasm of hepatocytes ≥300 mg/kg: mydriasis (M), ↓ body weight, ↓ food consumption (M), ↑ prothrombin time, ↑ APTT (F) 1000 mg/kg: ↓ food consumption (F), hypertrophy of thyroid follicular epithelium and proliferation of liver SER
Rat Fischer 344	Oral[a]	1 month	0; 100, 400 (prasugrel); 100 400 (clopidogrel)	10 M, 10 F	The effects of prasugrel and clopidogrel were similar and included ↓ body weight, ↓ red blood cell parameters, ↑ platelets, ↑ APTT, ↑ liver weight with hepatocellular hypertrophy, hypertrophy of thyroid follicular epithelium and proliferation of liver SER 400 mg/kg clopidogrel: regeneration of fibula epithelium and erythrocyte casts and acidophilic crystals in the renal tubular epithelium
Dog Beagle	Oral[b]	2 weeks	0, 100, 300, 1000	2 M, 2 F	≥100 mg/kg: mydriasis, vomiting, whitish substance in feces (considered unabsorbed test material), ↓ platelet aggregation, ↑ ALP, ↑ liver weight, hypertrophy and ground glass appearance of liver cells, atrophy of seminiferous epithelium in testes ≥300 mg/kg: ↓ body weight 1000 mg/kg: ↓ activity, ↑ ALT, ↓ hematopoietic cells in bone marrow Plasma concentrations of R-95913 increased with increasing dose and were greater on Day 14 than on Day 1
Dog Beagle	Oral[b]	1 month	0, 0.8, 4, 20, 100	2 M, 2 F	≥0.8 mg/kg: ↓ platelet aggregation ≥20 mg/kg: ↑ ALP, hypertrophy and ground glass appearance of liver cells, ↑ levels of cytochrome P450 content and conjugation enzymes 100 mg/kg: ↑ liver weight, inhibition of oxidative drug metabolism enzymes (MCD, ECD), proliferation of SER and formation of membrane whirls
Dog Beagle	Oral[b]	1 month	0; 50 (prasugrel); 4, 20, 50, 100 (clopidogrel)	2 M, 2 F	The effects of prasugrel and clopidogrel were similar and included ↓ platelet aggregation, ↑ ALP, ↑ cytochrome P450 content, ↓ ACD activity, ↑ liver weight with hepatocellular hypertrophy and ground glass appearance in hepatocellular cytoplasm and proliferation of liver SER ≥20 mg/kg clopidogrel: erosion, ulcer formation, and regeneration in the mucous membrane of the stomach.

= number, ↓ = decrease, ↑ = increase, ACD = alkoxycoumarin-dealkylase, ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate aminotransferase, APTT = activated partial thromboplastin time, ECD = ethoxycoumarin o-deethylase, MCD = methoxycoumarin o-demethylase, SER = smooth endoplasmic reticulum. [a] Vehicle = 0.5% (w/v) tragacanth gum solution. [b] Vehicle = None (test article administered as dry material in capsule).

2.6.7 Toxicology tabulated summary

Table 40. Effects of prasugrel in 3-month oral repeat-dose toxicity study in mice/B6C3F$_1$ (NOAEL 100 mg/kg)

Daily Dose (mg/kg)	0 (Control)		100		300		1000	
Sex:Number of Animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Noteworthy Findings								
Died or euthanized moribund	0	0	0	0	0	0	1	0
Body weight, g, Day 91 (% change[a])	30.0	26.3	↓3	↓2	↓7**	↓6*	↓15**	↓14**
Food consumption, cumulative average	–	–	–	–	–	–	–	–
Clinical signs (n[b])								
Fluorescent yellow urine	0	0	7	10	10	10	10	10
Ophthalmology	NE	NE	NE	NE	NE	NE	NE	NE
Enzyme induction	NE	NE	NE	NE	NE	NE	NE	NE
Hematology								
Red blood cell (10,000/μL)	929	949	879	943	911	866	862**	841**
Hemoglobin (g/dL)	15.4	15.8	14.6	15.7	15.1	14.5	14.2**	13.8**
Hematocrit (%)	47	48	45	49	47	45	44**	43**
Mean corpuscular volume (fL)	50.7	50.9	51.0	51.5*	51.3	52.2**	51.6*	51.6*
Mean corpuscular hemoglobin (%)	32.6	32.7	32.7	32.4	32.3	32.2**	32.0**	31.7**
Reticulocytes (%)	1.8	1.8	2.2	2.0	2.1	3.3	2.3*	2.8**
Clinical chemistry								
Alanine transaminase (IU/L)	26	32	29	32	33**	34	53**	38*
Alkaline phosphatase (IU/L)	150	261	139	223*	144	198**	118**	158**
Total protein (g/dL)	–	5.4	–	5.4	–	5.3	–	5.0**
Albumin (g/dL)	3.3	3.4	3.2	3.3	3.3	3.2	3.1**	3.1**
Albumin/globulin ratio	1.60	1.73	1.40**	1.63	1.54	1.58*	1.43**	1.61
Total cholesterol (mg/dL)	–	98	–	110*	–	110*	–	120*
Blood urea nitrogen (mg/dL)	30	23	28	22	28	22	21**	18**
Gross pathology (n[b])								
Liver								
Dark discoloration	0	0	0	0	0	0	9	9
Focus, white	0	0	0	0	0	0	1	0
Organ weight, mg/100 g BW, (% change[a])								
Liver	4.07	4.33	↑17**	↑12**	↑32**	↑30**	↑83**	↑82**
Spleen	–	292	–	↑2	–	↑17	–	↓21**
Kidney	1548	–	↓3	–	↓4	–	↓11**	–
Salivary gland	687.2	465.4	↑2	0	↓1	↑1	↓18**	↓14**
Ovary	NA	51.1	NA	0	NA	↓11	NA	↓38**
Uterus	NA	521	NA	↑4	NA	↓17	NA	↓25*
Histopathology (n[b])								
Adrenal								
Decreased X zone								
Slight	0	0	0	0	0	0	0	1
Mild	0	0	0	0	0	0	0	7
Hyperplasia, spindle cell								
Slight	4	8	2	8	1	9	0	4
Liver								
Hypertrophy, centrilobular								
Slight	0	0	0	0	10	9	0	0
Mild	0	0	0	0	0	0	9	10
Moderate	0	0	0	0	0	0	1	0

↑ = increase, ↓ = decrease, BW = body weight, NA = not applicable, NE = not evaluated, [a] For controls, group means and for treated groups percent differences from controls are shown, [b] Number of animals, * p≤0.05; ** ≤0.01.

Table 41. Effects of prasugrel in 6-month oral repeat-dose toxicity study in F344 rats (NOAEL 30 mg/kg)

Daily Dose (mg/kg)	0		10		30		100		300	
Sex:Number of Animals	M:15	F:15	M:15	F:15	M:15	F:15	M:15	F:15	M:15	F:15
Noteworthy Findings										
Died or euthanized moribund	0	0	0	0	1	0	0	1	0	0
Body weight, Day 182, g (% change[a])	289	164	↑1	↓1	↓3	↑1	↓11**	↓9**	↓26**	↓19**
Body weight gain, Days 1-182, g (% change[a])	201	74	↑1	0	↓4	↑3	↓17**	↓19**	↓42**	↓43**
Food consumption, Week 26, g/rat/day (% change[a])	15	10	0	0	0	0	↓7*	↓10*	↓13**	↓10**
Clinical signs (n[b])										
Yellow urine	0	0	0	0	14	15	15	15	15	15
Ophthalmology	–	–	–	–	–	–	–	–	–	–
Enzyme induction	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hematology										
Hemoglobin (g/dL)	16.3	16.7	16.2	16.1*	16.1	16.3	15.8**	15.9**	15.1**	15.0**
Mean corpuscular hemoglobin concentration (%)	33.3	34.0	33.1	33.7	33.3	33.7	32.9*	33.7	32.6**	33.5*
Platelets (10^4/µL)	63.5	62.1	64.7	62.0	66.2	63.9	68.4**	67.2**	78.9**	69.7**
Prothrombin time (sec)	13.7	12.0	13.3	11.8	13.9	11.5*	15.5	11.7	15.9*	12.1
Activated partial thromboplastin time (sec)	23.3	16.4	23.6	16.2	23.5	16.5	27.8*	17.5	34.0**	22.1**
Neutrophils (10^2/µL)	14.5	7.0	14.5	6.7	13.4	7.2	11.2	7.2	9.0**	5.1*
Fibrinogen (mg/dL)	202	151	195	162	204	152	220	168*	230**	149
Clinical chemistry										
Triglycerides (mg/dL)	80	–	74	–	72	–	57**	–	42**	–
Calcium (mg/dL)	9.7	9.6	9.8	9.6	9.9	9.8	10.0**	9.9**	10.2**	10.0**
Total cholesterol (mg/dL)	77	93	76	98	77	110**	72	113**	69*	98
Total bilirubin (mg/dL)	–	0.08	–	0.08	–	0.08	–	0.09	–	0.10**
Total protein (g/dL)	7.0	–	7.0	–	7.0	–	7.2**	–	7.6**	–
Albumin (%)	44.3	46.8	44.5	46.2	44.3	45.9	44.2	45.2*	45.6*	47.2
Globulin α1 (%)	19.9	–	19.8	–	19.2	–	18.9**	–	17.3**	–
Globulin α2 (%)	12.2	10.4	12.0	10.6	12.4	10.8	12.5	11.3**	13.2**	11.9**
Globulin β (%)	17.3	18.0	17.7	18.4	18.3**	18.5	18.9**	19.0*	19.1**	18.4
Globulin τ (%)	6.2	7.6	5.9	7.4	5.8	7.5	5.5*	7.0*	4.7**	6.3**
Urinalysis[b]										
Urobilinogen: (≥+)	3	2	6	7	10	9	12	11	7	8
Gross pathology	–	–	–	–	–	–	–	–	–	–
Organ weight, absolute, g (%change[a])										
Thymus	85	89	↑4	0	↑1	↓3	↓7	↓18**	↓28**	↓34**
Spleen	0.55	0.37	↓2	↓3	↓5*	↓5	↓16**	↓16**	↓33**	↓32**
Prostate	0.62	NA	↑2	NA	↓5	NA	↓29**	NA	↓44**	NA
Liver	6.84	3.60	↑4	↑2	↑4	↑7*	↑8*	↑11**	↑18**	↑19**
Uterine	NA	550	NA	↑1	NA	0	NA	↓14	NA	↓37**
Histopathology (n[b])										
Liver										
Hypertrophy										
Slight	0	0	0	0	0	7	13	14	0	0
Mild	0	0	0	0	0	0	2	1	15	15
Adrenal										
Decreased lipid content, zona granulosa cell										
Slight	1	0	0	0	2	0	0	2	13	10

↓ = decreased, ↑ = increased, - = no important findings, NA = not applicable, NE = not evaluated, [a] for controls, group means, and for treated groups, percent differences from controls are shown, [b] Number of animals, * p≤0.05; ** ≤0.01

Table 42. Effects of prasugrel in 9-month oral repeat-dose toxicity study in beagle dogs (NOAEL 4 mg/kg)

Daily Dose (mg/kg)	0 (Control)		0.8		4		20	
Sex:Number of Animals	M:6	F:6	M:4	F:4	M:6	F:6	M:6	F:6
Noteworthy Findings								
Died or euthanized moribund	0	0	0	0	0	0	0	0
Body weight	–	–	–	–	–	–	–	–
Food consumption	–	–	–	–	–	–	–	–
Clinical chemistry, Month 9								
Alkaline phosphatase (IU/L)	127	116	118	92	128	155	257**	240*
Hepatic and renal function	–	–	–	–	–	–	–	–
Histopathology (n[b])								
Liver								
Centrilobular hypertrophy								
Slight	0	0	0	0	0	0	1	0
Mild	0	0	0	0	0	0	1	0
Electron microscopy (liver)								
Reversibility Evaluations								
Clinical chemistry								
Alkaline phosphatase (IU/L)	110	112	NA	NA	94	122	173	122
Histopathology (n[b])								
Liver								
Centrilobular hypertrophy	0	0	NA	NA	0	0	0	0

- = no important findings, NA = not applicable, NE = not evaluated, [a] Two animals in each sex/group were reversal animals, [b] Number of animals or tissues, * p≤0.05; ** ≤0.01

Table 43. Effects of prasugrel in a 2-year carcinogenicity study in rats

Daily Dose (mg/kg)	0 (Control)		10		30		100	
Sex:Number of Animals	M:55	F:55	M:55	F:55	M:55	F:55	M:55	F:55
Histopathology: neoplastic lesions (n[b])								
Adrenal								
Adenoma, cortical cell	0	1	0	0	0	0	0	0
Ganglioneuroma	0	0	0	0	0	1	0	0
Pheochromocytoma	3	3	2	0	3	2	0	3
Pheochromocytoma, malignant	2	2	2	0	2	0	2	0
Carcinoma, cortical cell	1	1	0	0	0	0	0	1
Hemolymphoreticular (all sites):								
Lymphoma, malignant	0	1	0	0	0	0	0	0
Sarcoma, histiocytic	1	1	0	1	0	1	0	0
Leukemia, large granular lymphocytic	8	14	8	13	3	6	2	1
Liver:								
Adenoma, hepatocellular	2	0	4	0	0	0	1	0
Carcinoma, cholangiocellular	0	0	0	1	0	0	0	0
Lung (bronchus):								
Adenoma, bronchiolo-alveolar	2	1	3	0	1	3	1	3
Carcinoma, bronchiolo-alveolar	0	0	1	0	1	0	1	0
Pancreas:								
Adenoma, islet cell	8	1	8	2	8	2	9	2
Adenoma, acinar-islet cell	0	0	2	0	0	0	0	0
Pituitary:								
Adenoma, anterior	11	17	13	15	18	17	7	17
Carcinoma, anterior	0	0	0	0	0	1	0	1
Thyroid:								
Adenoma, C-cell	13	7	9	7	11	4	10	9
Carcinoma, C-cell	2	4	1	3	5	3	0	4
Carcinoma, follicular cell	1	0	1	0	0	0	1	0
# of tumor-bearing animals (incidence)	54/98	43/78	54/98	44/80	55/100	46/84	55/100	47/85
Benign	52	37	52	39	51	37	52	44
Malignant	18	31	21	21	19	25	9	15
Benign and malignant	16	25	19	16	15	16	6	12
Liver								
Hypertrophy, hepatocytic, diffuse								
Minimal	0	0	0	0	0	0	20	15
Altered cell focus, eosinophilic								
Minimal	43	26	39	30	42	30	40	35
Mild	0	1	2	0	2	1	11	1
Moderate	0	0	0	1	0	0	0	0

= number, ↑= increase, ↓= decrease [a] For controls, group means, and for treated groups, percent differences from controls are shown , [b] Number of animals or tissues, [c] Only tissues with a gross lesion .

Table 44. Effects of prasugrel in a 2-year carcinogenicity study in mice

Daily Dose (mg/kg)	0 (Control)		30		100		300	
Sex:Number of Animals	M:55	F:55	M:55	F:55	M:55	F:55	M:55	F:55
Histopathology: neoplastic lesions (n[b])								
Liver:	55	55	55	55	55	55	55	55
Adenoma, hepatocellular	20	5	11	5	26	20**[d]	44**[d]	39**[d]
Hemangioma	6	1	3	2	1	0	1	0
Carcinoma, hepatocellular	11	1	12	4	13	2	16	5
Hemangiosarcoma	0	1	3	2	1	0	0	0
Hepatoblastoma	0	0	0	0	0	1	1	0
Histopathology: neoplastic lesions (n[b])								
Liver:	55	55	55	55	55	55	55	55
Adenoma, hepatocellular	20	5	11	5	26	20**[d]	44**[d]	39**[d]
Hemangioma	6	1	3	2	1	0	1	0
Carcinoma, hepatocellular	11	1	12	4	13	2	16	5
Hemangiosarcoma	0	1	3	2	1	0	0	0
Hepatoblastoma	0	0	0	0	0	1	1	0
Hemolymphoreticular (all sites):								
Lymphoma, malignant	4	14	9	22	3	13	5	12
Sarcoma, histiocytic	1	5	3	2	1	7	1	4
Lung (bronchus):								
Adenoma, bronchiolo-alveolar	5	1	5	2	5	4	6	3
Carcinoma, bronchiolo-alveolar	3	2	3	2	8	1	4	2
Hemangiosarcoma	1	0	0	0	0	0	0	0
Osteosarcoma	0	1	0	0	0	0	0	0
Lymph node, nos (number evaluated)[c]:	2	7	8	13	5	11	3	10
Hemangiosarcoma	0	0	0	0	1	0	0	0
# of tumor-bearing animals (incidence)	42/76	37/67	36/65	42/76	39/71	44/80	52/95	50/91
Benign	33	17	22	24	29	32	45	45
Malignant	19	29	26	32	25	27	25	28
Benign and malignant	10	9	12	14	15	15	18	23
Histopathology: nonneoplastic lesions (n[b])								
Liver								
Hypertrophy, hepatocytic, central								
Minimal	0	0	0	0	7	0	6	0
Mild	0	0	0	0	2	0	9	0
Moderate	0	0	0	0	0	0	7	0
Altered cell focus, eosinophilic	9	6	17	6	23	18	24	36
Thyroid								
Hypertrophy, follicular cell								
Minimal	0	1	0	0	1	0	19	9
Mild	0	0	0	1	0	1	0	0
Pigmentation, follicular cell								
Minimal	0	1	1	2	5	6	23	25
Mild	0	0	0	1	0	1	5	4
Moderate	0	0	0	0	0	0	0	1

= number, ↑ = increase, ↓ = decrease, – = no important findings, NA = not applicable,
[a] For controls, group means, and f or treated groups, percent differences from controls are shown,
[b] Number of animals or tissues, [c] Only tissues with a gross lesion , [d] For incidental and fatal tumors.

Table 45. Effects of prasugrel on fertility and early embryonic development to implantation in rat
Males 4 weeks prior to and through mating, and females 2 weeks prior to mating through GD 7

	Daily Dose (mg/kg)	0 (Control)	30	100	300
Males	Toxicokinetics	NE	NE	NE	NE
	Number evaluated	24	24	24	24
	Number died or euthanized moribund	0	0	0	1
	Clinical observations (n[a])				
	Salivation	0	0	18	21
	Yellow staining of tray paper	0	0	24	24
	Necropsy observations	–	–	–	–
	Body weight gain, g, Days 0-28 (premating) (% change[b])	99	↓3	↓10*	↓45**
	Body weight gain, g, Days 28-63 (% change[b])	90	↑1	↑3	↓22**
	Food consumption, cumulative, g/rat, Days 1-28 (% change[b])	805	0	↓1	↓7**
	Mean number of days prior to mating	2.0	2.5	3.0	2.0
	Number of males that mated	22	24	23	23
	Number of fertile males	23	24	23	23
	Sperm motility/count				
Females	Toxicokinetics	NE	NE	NE	NE
	Number evaluated	24	24	24	24
	Number died or euthanized moribund	0	0	0	0
	Clinical observations (n[a])				
	Pupil dilation	0	0	11	24
	Salivation	0	0	5	21
	Yellow staining of tray paper	0	24	24	24
	Body weight gain, g, (% change[b])				
	Premating Days 1-14	26	↓12	↓35**	↓65**
	Gestation Days 0-8	42	↑5	↓1	↓26**
	Gestation Days 8-15	47	0	↑10	↑17**
	Food consumption, cumulative, g/rat, Days 15-28 (% change[b])	274	0	↑1	↓7*
	Necropsy observations				
	Mating index (%)	92	100	96	100
	Fertility index (%)	92	100	96	100
	Number of live fetuses/litter	16.3	15.0	16.0	15.9
	Number early in utero deaths	0.8	1.1	0.9	0.6
	Number late in utero deaths	0.1	0	0.1	0
Females (concluded)	Number early and late in utero deaths	0.9	1.1	1.0	0.6
	Mean number corpora lutea/dam	18.2	18.3	19.2	17.5
	Mean number implantation/dam	17.2	16.2	17.0	16.5
	Mean preimplantation loss/litter	1.0	2.2	2.2	1.0

↑ = increase, ↓ = decrease, – = no important findings, NE = not evaluated. [a] Number of animals or tissues.
[b] control group means, treated groups percent differences from controls are shown. *p≤05, **p≤.01.

Table 46. Effects of prasugrel on embryo-fetal development in rat during GD 7 through GD 17

	Daily Dose (mg/kg)	0 (Control)	30	100	300
Dams	Toxicokinetics	NE	NE	NE	NE
	Number pregnant	23	24	24	24
	Number died or euthanized moribund	0	0	1[a]	0
	Number aborted or with total resorption of litter	0	0	0	0
	Clinical observations (n[b])				
	Pupil dilation	0	0	15	22
	Necropsy observations				
	Body weight gain, g (% change[c])				
	Gestation Days 8 – 14	41.4	↓1	↓10*	↓29**
	Gestation Days 18 – 20	33.6	↑4	↑3	↑24**
	Food consumption, g/rat/day (% change[c])				
	Gestation Day 7	25	↓4	↓12**	↓32**
	Gestation Days 8 – 9	26	↓4	↓12**	↓15**
	Gestation Days 10 – 11	27	↓4	↓7*	↓11*
	Gestation Days 12 – 13	27	↓4	↓4	↓7**
Dams, concluded	Mean number corpora lutea/dam	15.5	16.3	14.9	16.3
	Mean number implantations/dam	13.7	14.7	14.0	15.1
Litters	Number of litters evaluated	23	24	23	24
	Number of in utero deaths/litter (early)	0.9	0.8	0.9	0.8
	Number of in utero deaths/litter (late)	0.5	0.1	0.1	0.0*
	Number of live fetuses/litter	12.2	13.8	13.0	14.3**
	Fetal weight (grams, gender combined)	3.8	3.8	3.7	3.6*
	Litter weight (grams, gender combined)	45.9	51.8	48.3	51.0
	Fetal sex ratios (% male)	50.7	51.5	48.9	50.9

↑ = increase, ↓ = decrease, NE = not evaluated, [a] Rat found dead on Gestation Day 20 (bleeding), [b] Number of animals or tissues.

Table 47. Effects of prasugrel on embryo-fetal development in NZW rabbit during GD 6 through GD 18

	Daily Dose (mg/kg)	0 (Control)	30	100	300
Dams	Number pregnant	19	19	19	19
	Number died or euthanized moribund	0	0	1[a]	0
	Number aborted or with total resorption of litter	0	0	0	0
	Clinical observations (n[b])				
	Yellow urine	0	0	0	6
	Necropsy observations	..	..	..	..
	Body weight				
	Gestation Day 9	3.748	3.731	3.737	3.666
	Gestation Day 15	3.896	3.895	3.893	3.748
	Gestation Day 21	3.973	3.957	3.980	3.815
	Gestation Day 28	4.103	4.064	4.058	3.961
	Food intake, g				
	Gestation Days 6-7	150	149	150	136**
	Gestation Days 10-11	150	149	148	119**
	Gestation Days 14-15	143	145	132	94**
	Gestation Days 18-19	142	144	140	112**
	Mean number corpora lutea/dam	9.3	9.4	9.3	8.9
	Mean number implantations/dam	8.5	8.1	7.5	7.9
Litters	Number of litters evaluated	19	19	19	19
	Number of live fetuses/litter	7.6	7.5	7.0	7.2
	Number of early resorptions/litter	0.2	0.1	0.1	0.1
	Number of late resorptions/litter	0.5	0.3	0.2	0.4
	Number of dead fetuses/litter	0.2	0.3	0.3	0.2
	Body weight of live male fetuses (g)	39.4	40.9	40.2	37.5
	Body weight of live female fetuses (g)	38.6	39.0	39.4	37.3
	Sex ratio (%male/%female)	50/50	51/49	51/49	47/53
Litters	Fetal anomalies				
	Gross external (number of fetuses [litters] examined)	145 [19]	142 [19]	133 [19]	137 [19]
	Absent eye bulge	0 [0]	0 [0]	1 [1]	0 [0]
	Misshapen nose	0 [0]	0 [0]	1 [1]	0 [0]
	Naris atresia	0 [0]	0 [0]	1 [1]	0 [0]
	Paw hyperflexion	0 [0]	0 [0]	0 [0]	1 [1]

GD = Gestation Day, NA = not applicable, NE = not evaluated, [a] Non treatment-related death.
[b] Number of animals or tissues, *p≤05, **p≤.01 (Dunnett's rank test).

Table 48. Effects of prasugrel on pre- and postnatal development in rats during gestation day 6 through lactation Day 20

	Daily Dose (mg/kg)	0 (Control)	30	100	300
F_0 females	# pregnant	22	22	22	22
	# died or euthanized moribund	0	0	0	0
	# aborted	0	0	0	0
	Clinical observations				
	Post-dosing salivation				
	Animals with the finding	0	7	20	22
	Total number of occurrences	0	9	99	243
	Rubbing of muzzle on bottom of cage				
	Animals with the finding	0	0	4	11
	Total number of occurrences	0	0	5	13
	Abnormal yellow staining of the cage tray paper				
	Animals with the finding	0	0	21	22
	Total number of occurrences	0	0	41	65
	Necropsy observations (animals with the finding)				
	Mandibular lymph node: Enlarged	1	0	0	0
	Liver: Pale area on left lobe	0	0	1	0
	Caecum: Distended with gas and pale fluid	0	0	0	1
	Body weight (g), Gestation Day 20 (% change)[a]	406	–	↓2.7	↓7.6**
	Body weight (g), Lactation Day 21 (% change)[a]	340	–	↓2.9	↓11.5**
	Food consumption (g/rat/day), GD 6-9 (% change)[a]	28	–	↓3.6	↓17.9**
	Food consumption (g/rat/day), GD 18-19 (% change)[a]	31	–	–	↓6.5
	Food consumption (g/rat/day), LD 4-6 (% change)[a]	53	–	↓4.0	↓13.5**
	Food consumption (g/rat/day), LD 11-13 (% change)[a]	76	–	↓5.3	↓17.1**
	Mean duration of gestation (days)	22.3	22.2	22.3	22.6**
F_1 litters	# of litters evaluated	22	22	21[b]	22
Preweaning	Mean # of implantations	15.4	15.5	15.2	15.5
	Mean # pups/litter	14.3	14.5	14.2	14.5
	Mean # liveborn pups/litter	14.2	14.2	14.0	14.0
	Mean # stillborn pups/litter	0.1	0.2	0.2	0.5
	# of litters with stillborn pups	3	5	4	6
	Postnatal survival to Day 4	14.2	14.0	13.8	13.8
	Postnatal survival to weaning (after cull)	9.9	9.8	9.7	9.9
	# of total litter losses	0	0	1	0
	# live newborn pups with external anomalies	0	0	0	0
	Pup body weight (g), (% change)[a]				
	Newborn				
	Male	6.9	↓4.3	↓2.9	↓8.7**
	Female	6.5	↓4.6	↓3.1	↓9.2**
	Change from birth to weaning				
	Male	41.0	↓0.2	↓0.2	↓20.0**
	Female	40.0	↓1.0	↓0.8	↓19.8**
	Pup sex ratio on Day 1 (% males)	50.9	53.8	51.4	47.3
F_1 females	Premating body weight change (% change)[a]	0.0	↓1.3	↓1.3	↓1.3
Postweaning	Gestation body weight change (% change)[a]	0.0	0.0	↓1.2	↑1.2
	Vaginal opening (day of attainment)	34.7	36.0	35.1	36.3*
	Motor activity (high beam total)	163.5	200.7	114.9	184.0
	(low beam total)	596.7	640.4	426.2	586.1
	Accelerating rotarod (maximum time)	202	206	199	228*
	Morris maze (trial time on Day 4)	14.2	13.1	14.1	13.0
	Mean # days prior to mating	2.8	2.6	2.4	2.5
	# of females copulated	20	20	20	20
	# of pregnant females	20	20	20	19
	# aborted	0	0	0	0
	Mean # corpora lutea	16.6	16.7	17.1	15.4
	Mean # implantations	15.4	14.8	14.6	14.6
F_2 litters	Mean # live conceptuses, Gestation Day 14	14.5	13.7	14.0	14.0
	Mean # of resorptions	0.9	1.2	0.7	0.6
	Mean % preimplantation loss	7.9	11.2	16.0	7.1
	Mean % postimplantation loss	5.4	8.2	4.0	4.1
	# Total litter losses	0	0	0	0

= number, ↑ = increase, ↓ = decrease, NA = not applicable, [a] For controls, group means, and for treated groups, percei differences from controls are shown, [b] Data from 1 dam in the 100 mg/kg group are excluded because of total litter loss.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The pharmacological and toxicological documentation provided are appropriate and adequate from a preclinical perspective to support the intended clinical use of prasugrel at a daily dose of 10 mg. Bleeding is a potential risk which may be expected with prasugrel due to the mechanism of action of inhibition of platelet aggregation.

Unresolved toxicology issues:

- Prasugrel causes induction of cytochrome P450 of phase I drug-metabolizing enzymes (primarily Cyp2B, Cyp3A2), and phase II drug-metabolizing enzymes (UDP glucuronosyl transferase and glutathione S-transferase), which is consistent with the decreases in exposure to prasugrel metabolites after multiple dosing. No specific animal studies have been conducted on the effects of induction of drug metabolizing enzymes and interaction with other drugs metabolized via Cyp2B and cyp3A.

Recommendations: Approvable

Suggested labeling:

b(4)

b(5)

Signatures (optional):

Pharm/Tox Reviewer _____

Concurring Reviewer _____

APPENDIX/ATTACHMENTS

- Exec-CAC meeting minutes for protocol dose selections.
- Exec-CAC final study minutes.