2.6.4.5 Metabolism

Prasugrel, which contains one chiral center, is rapidly hydrolyzed *in vivo* by esterases in the intestine to a thiolactone, R-95913, which contains two chiral centers (Figure 15). R-95913 is absorbed via portal vein, and is subsequently metabolized by several cytochrome P450 (CYP) enzymes, mainly CYP3A and CYP2B6, to the thiol-containing active metabolite, R-138727. The intestinal esterases, including carboxylesterases and CYP3A, the major CYP in the intestine, play a significant role in the rapid formation of the active metabolite in plasma (R-138727). R-138727 is further metabolized by S-methylation to R-106583 and by conjugation with cysteine to R-119251. An isomer of the thiolactone is also metabolized producing another thiol containing molecule, R-104434. R-138727 has two chiral centers, and its four enantiomers have differing degrees of pharmacological activity (Figure 18). The thiol compounds are metabolized further by S-methylation to R-106583 and R-100932 and by formation of the cysteine conjugates, R-119251 and R-118443. Several other metabolites of prasugrel found were formed through oxidation, conjugation with glucuronic acid, or a combination of both pathways (Figure 18). The metabolites R-95913, R-106583, and R-119251 are pharmacologically inactive. The active metabolite, R-138727, and the major human metabolite, R-106583, represent the significant moieties in terms of pharmacologic activity and relative abundance, respectively.

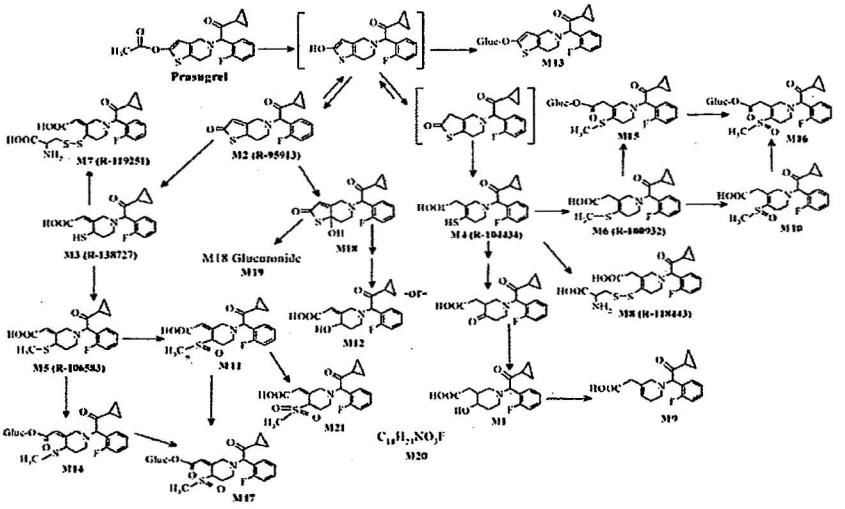

Figure 18. Possible metabolic pathway for prasugrel
(Brackets indicate compounds are postulated and have not been detected)

2.6.4.6 Excretion

Rats administered 5 mg/kg oral dose of ^{14}C-prasugrel eliminated about 90% in the feces and 7% in the urine. The parent compound was not detected in the feces or urine up to 24 h. Metabolites R-106583 and R-100932 accounted for 11.5% and 7.4% of the radioactivity in the feces, respectively. R-119251 was not excreted in the feces though it existed in the bile, suggesting a possibility that R-119251 is further metabolized and then

excreted in the feces or re-absorbed from the digestive tract. R-106583 was detected in the bile and feces after enzymatic hydrolysis, suggesting that R-106583 is excreted in the bile as glucuronide and hydrolyzed to R-106583 again in the digestive tract. Metabolites R-118443 and R-119251 accounted for 14.5% and 9%, respectively, of the radioactivity in the urine. Unknown metabolites accounted for 24%. Biliary excretion appears to be the major route for elimination of prasugrel and its metabolites in rats and dogs (73 - 79% in feces), mice tended to eliminate more in the urine (53%). Prasugrel metabolites identified in human plasma, urine, and feces were also identified in the animals (Table 4).

Table 4. Prasugrel metabolites in plasma, urine, and feces

	Mouse			Rat			Dog			Human		
Metabolite ID[a]	Plasma	Urine	Feces	Plasma	Urine	Feces	Plasma	Urine	Feces	Plasma	Urine	Feces
M1	X	X	X	X	X	X	X	X	X	X	X[c]	X
M2 (R-95913)	X	-	X	X	X	X	X	X	X	X	-	-
M3 (R-138727)	X	X	-	X	-	-	X	-	-	X	-	-
M4 (R-104434)	X	-	-	X	-	-	X	-	-	X	-	-
M5 (R-106583)	X[b]	X	X[b]	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X	X[b]
M6 (R-100932)	X	X	X	X[b]	X	X	X[b]	X[b]	X	X	X	X
M7 (R-119251)	X	X	-	X	-	-	X	X	-	X	X	-
M8 (R-118443)	-	-	-	-	-	-	X	-	-	X	X	-
M9	X	X	X	X	X	X	X	X	X	X	X	X
M10	X	X	X	X	X	X	X	X	X	X	X	X
M11	X	X[b]	X	X	X[b]	X	X	X	X	X	X	X
M12	-	X	-	X	X	X	X	X	X	-	X	-
M13	X	X	-	-	-	-	X	X	-	X	X	-
M14	X	X	-	X	-	-	X	X	-	X	X	-
M15	X	X	-	X	-	-	X	X[b]	-	X	X	-
M16	X	X	-	-	-	-	-	-	-	X	X	-
M17	X	X	-	-	-	-	-	-	-	X	X	-
M18	-	X	-	-	-	-	X	X	X	X	X	-
M19	X	X	-	-	-	-	X	X	-	X	X	-
M20	-	-	-	-	-	-	-	X	-	-	X	-
M21	X	X	X	-	X	X	-	-	X	-	-	-

2.6.4.7 Pharmacokinetic drug interactions

No specific animal studies have been conducted to evaluate drug-drug interactions.

2.6.4.8 Other pharmacokinetic studies

Prasugrel on hepatic drug metabolizing enzyme system in rats:

Prasugrel (1, 10, 100 and 300 mg/kg) administered orally once daily for 7 days to rats caused increase in cytochrome b_5 content and glutathione S-transferase activity per mg microsomal, and liver (by 17 - 23%) at doses ≥ 10 mg/kg (Table 5). In the 100 and 300 mg/kg, the cytochrome P450 content, b5 content and activities per mg microsomal or cytosol protein were increased, but no significant difference was observed in the microsomal protein content or cytosol protein content from the control group. Prasugrel at doses > 10 mg/kg has an induction effect on cytochrome P450 of phase I drug-metabolizing enzymes (primarily CYP2B, CYP3A2), and phase II drug-metabolizing enzymes (UDP glucuronosyl transferase and glutathione S-transferase). These observations are consistent with the decreases in exposure to prasugrel metabolites observed in the rat and dog with multiple dosing, and the morphologic hepatic changes observed suggesting possible induction of drug metabolizing enzymes (Section 2.6.4.10., Tables 6 and 7).

Table 5. Liver P450 isoforms induced after 7 days administration of prasugrel to F344 rat (n=5/group)

	P450 Content (Percent of Control)[a]				
	Prasugrel				Phenobarbital
Enzyme measured	1 mg/kg	10 mg/kg	100 mg/kg	300 mg/kg	80 mg/kg
CYP1A2	91	92	77	71	69
CYP2B	90	96	171	199	280
CYP2C6	112	103	126	114	158
CYP2C11	97	95	89	88	94
CYP2C13	76	74	74	97	100
CYP2E1	60	79	99	69	83
CYP3A2	98	114	148	126	159
CYP4A	108	90	111	107	98

R-95913 on CYP1A2 and CYP3A in culture human hepatocytes:

In primary cultures of human hepatocytes, R-95913 (0.1 to 100 μM for 72 h) caused induction of Cyp3A, but not Cyp1A2. In these studies, omeprazole and rifampicin were used as positive inducers of Cyp1A2 and Cyp3A, respectively. Cyp3A and Cyp1A2 are known to be major inducible human isoforms.

Milk transfer of ^{14}C-prasugrel in rats:

After single oral administration of ^{14}C-prasugrel to lactating rats at a dose of 5 mg/kg, the ratios of the radioactivity concentration in the milk to that in the plasma were 4.7 at 4 h and 1.7 at 24 h, suggesting transfer of prasugrel or its metabolites into the milk (Table 6). The radioactivity from the milk was eliminated more rapidly than that from the plasma, and the radioactivity concentration in the milk had decreased to less than 1% of the 1-h value at 72 h, suggesting that the radioactivity did not remain in the milk over a long period.

Table 6. Excretion into milk of ^{14}C-prasugrel base in pregnant or nursing F344 rat

Time (hour)	1	2	4	8	24	48	72
Milk (ng-eq/mL)	2258 ± 594	2234 ± 583	1937 ± 390	1545 ± 413	470 ± 78	52 ± 22	17 ± 3
Plasma (ng-eq/mL)	1314 ± 279	619 ± 115	405 ± 111	385 ± 121	218 ± 30	90 ± 10	36 ± 7
Milk/Plasma (%)	1.72	3.61	4.78	4.01	2.16	0.58	0.47

2.6.4.9 Discussion and Conclusions

Prasugrel, a prodrug, is rapidly metabolized by de-esterification, forming a thiolactone (R-95913, inactive metabolite), followed by ring opening to form the sulfhydryl compounds R-104434 (inactive) and R-138727 (active). R-138727 has two chiral centers, and only the enantiomers of R-138727 are active pharmacologically. The sulfhydryl compounds are further metabolized by S-methylation catalyzed by cytochrome P450 (CYP3A4 and other CYP isoforms) to R-106583 and R-100932, and by formation of cysteine conjugates, R-119251 and R-118443 (inactive metabolites). The AUC values for the metabolites decreased after daily oral dosing compared to the values obtained after the first dose suggesting possible induction of drug metabolizing enzymes (CYP2B and CYP3A2). Biliary excretion appears to be the major route for elimination of prasugrel and its metabolites. The elimination $t_{1/2}$ is 10 h and 33 h in the rat and dog, respectively. In humans, R-106583 is the major metabolite detected beyond 12 hrs after oral administration of prasugrel.

2.6.4.10 Tables and figures to include comparative TK summary

Table 7. Metabolite exposures after repeated daily oral doses of prasugrel.HCl and prasugrel.base in rats

Metabolite	Dose[a] (mg/kg)	First Dose C_{max} (µg/mL) M	First Dose C_{max} (µg/mL) F	First Dose AUC_{0-24} (µg*h/mL) M	First Dose AUC_{0-24} (µg*h/mL) F	Day 28 C_{max} (µg/mL) M	Day 28 C_{max} (µg/mL) F	Day 28 AUC_{0-24} (µg*h/mL) M	Day 28 AUC_{0-24} (µg*h/mL) F
R-106583	30	1.17	2.08	5.59	5.84	1.22	2.67	5.44	11.13
	100	4.70	3.63	24.77	24.22	2.46	6.69	12.46	31.66
	300	13.28	10.71	111.0	150.9	5.90	16.26	30.93	80.74
	300 base	12.44	10.82	153.3	128.4	5.75	13.50	33.37	109.2
R-138727	30	3.21	7.46	6.72	15.0	2.85	5.42	5.02	9.55
	100	13.1	12.2	44.3	49.2	8.80	17.3	22.3	39.1
	300	32.8	21.1	175	181	22.6	37.4	60.6	93.2
	300 base	31.9	19.0	193	153	19.9	26.9	62.5	103

Table 8. Metabolite exposures after daily oral doses of prasugrel.HCl and prasugrel.base in dogs

Metabolite	Dose[a] (mg/kg)	C_{max} (µg/mL) Day 1 M	C_{max} (µg/mL) Day 1 F	C_{max} (µg/mL) Day 28 M	C_{max} (µg/mL) Day 28 F	AUC_{0-24} (µg*h/mL) Day 1 M	AUC_{0-24} (µg*h/mL) Day 1 F	AUC_{0-24} (µg*h/mL) Day 28 M	AUC_{0-24} (µg*h/mL) Day 28 F
R-106583	4	0.164	0.187	0.135	0.177	0.438	0.867	0.445	0.650
	20	0.616	1.51	0.518	0.647	2.84	5.08	2.42	2.06
	100	1.57	2.11	0.766	1.45	11.7	22.0	7.58	11.5
	100 Base	0.706	1.56	0.965	0.659	4.17	10.9	6.61	4.84
R-138727	4	1.12	0.98	0.74	1.02	1.66	1.78	1.01	1.42
	20	3.20	5.91	3.02	3.07	7.44	10.7	6.56	5.74
	100	6.05	15.6	5.14	6.04	24.1	46.0	21.4	27.7
	100 Base	2.40	4.45	4.97	3.27	8.67	17.1	17.3	14.3

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Table 9. Plasma metabolites after single oral 5 mg prasugrel base and its salt form in SD rat (n=11)

		Prasugrel Metabolite R-119251	R-118443	R-106583	R-100932	R-95913	R-138727
Prasugrel Base							
AUC_{0-8}	ng•hr/mL	4650	176	1470	2330	27.6	2630
C_{max}	ng/mL	1730	68.8	392	651	19.9	992
Prasugrel HCl							
AUC_{0-8}	ng•hr/mL	5710	313	1390	2330	25.0	3390
C_{max}	ng/mL	2310	239	501	730	55.6	1550

Table 10. Plasma metabolites after single oral 2 mg prasugrel base and its salt form in beagle dog (n=6)

		Metabolite R-119251	R-118443	R-106583	R-100932	R-95913	R-138727
Prasugrel Base							
AUC_{0-8}	ng•hr/mL	672	65.8	196	113	244	979
C_{max}	ng/mL	472	33.6	119	50.5	137	798
Prasugrel HCl							
AUC_{0-8}	ng•hr/mL	738	71.2	285	136	324	1050
C_{max}	ng/mL	611	42.1	188	73.3	230	1020

2.6.6 TOXICOLOGY

2.6.6.1 Overall general toxicology summary

In mice, repeated oral administration of prasugrel for 3-months at doses ≥ 300 mg/kg caused increased liver weight, hypertrophy of the centrilobular hepatocytes and diffuse hepatocyte vacuolation. In rats repeated oral administration of prasugrel for 3- and 6-months at doses ≥ 100 mg/kg was associated with increased liver weight, hepatocellular hypertrophy, hypertrophy of thyroid follicular epithelium and proliferation of smooth endoplasmic reticulum, changes consistent with microsomal enzyme induction. In dogs repeated oral administration of prasugrel for 3- and 9-months at doses > 4 mg/kg/day was associated with increase in ALP levels, hypertrophy of hepatocytes accompanied by ground glass appearance of the liver, and proliferation of smooth-surfaced endoplasmic reticulum. These changes may be due to an activation of drug metabolism enzymes. The AUC of the metabolite R-106583 at the NOAEL of the mice, rat and dog (100, 30 and 4 mg/kg, respectively) were 200-, 18- and 1.5-fold higher than that projected in human plasma levels (Section 2.6.6.10. Tabulated Summary, Tables 38 and 39).

2.6.6.2 Single-dose toxicity

Single-dose toxicity in mouse RFVL:

No mouse died after receiving 2000 mg/kg of prasugrel free base by oral gavage in the 14-day observation period (n=10 M, 10 F). There were no adverse effects observed in the gross pathological examinations at termination.

Single-dose toxicity in F344 rat:

No rat died following administration of 1000 or 2000 mg/kg of prasugrel free base by oral gavage observed for 14-days (n=5/sex/group). In the prasugrel HCl salt groups, 3/5 males and 4/5 females died at 2000 mg/kg. Excretion of fluorescent yellow urine originated from metabolites of the test article was observed in all the prasugrel HCl and prasugrel base groups. Clinical signs that were apparent include mydriasis and decreased spontaneous movement in the prasugrel base groups at ≥ 1000 mg/kg, and the prasugrel HCl 2000 mg/kg group. In females in the prasugrel HCl 2000 mg/kg dose group, in which deaths occurred, some animals showed prone/lateral position. There were no adverse effects observed in gross pathological examination at termination. Comparison of AUC0-24h between prasugrel HCl and prasugrel base groups at 2000 mg/kg revealed that the concentrations of all metabolites were about 1.5 times higher in the prasugrel HCl group than in the prasugrel base group, and the enhanced mortality with the latter may be related to the differences in the concentrations of metabolites (Table 11).

Table 11. Exposure parameters for metabolite R-106583 in the rat

Prasugrel HCl salt			Prasugrel free base		
Dose	AUC_{0-24} (μg.h/ml)		Dose	AUC_{0-24} (μg.h/ml)	
(mg/kg)	Male	Female	(mg/kg)	Male	Female
1000	796	973	1000	511	497
2000	1100	1048	2000	530	525

Single-dose toxicity in Beagle dogs:

Two dogs administered escalating doses of prasugrel free base (30, 100, 300, 1000 and 2000 mg/kg) showed emesis at higher doses (≥300 mg/kg), increased serum alkaline phosphatase (ALP) and hepatocellular atrophy at necropsy in the high dose 2000 mg/kg (n=1 M, 1 F). At ≥ 300 mg/kg, platelet aggregation was decreased. The test compound was observed in the vomitus after the administration at 1000 mg/kg, and toxicity was not evaluated at doses above 1000 mg/kg.

2.6.6.3 Repeat-dose toxicity

3-month repeat-dose in mice:

Key findings: In mice repeated oral administration of prasugrel for 3-months at doses ≥ 300 mg/kg/day caused hypertrophy of the centrilobular hepatocytes (+14 to +58%), increased liver weight, diffuse hepatocyte vacuolation, decrease weight of the ovary, uterus (-11 and -38%), spleen (-32%) and kidneys. The AUC of the major human metabolite (R-106583) at the NOAEL (100 mg/kg) was about 200-fold higher than that projected in human plasma levels (Section 2.6.7. Tabulated Summary: Table 40).

Study no.:	APRC-149-045, B-4593		
Conducting laboratory:	[redacted]		
Date of study initiation:	Oct 27, 2000,	**Final report:**	April 19, 2002
GLP compliance:	Yes,	**QA report:**	yes (√), no ( )
Drug:	Prasugrel		
Doses:	100, 300 and 1000 mg/kg/day, Vehicle tragacanth 0.5%		
Species/strain:	Crj:B6C3F1 Mice		
Number/sex/group:	10/sex/dose group		
Route:	Oral gavage		

b(4)

Results:

Mortality: One male mice (1/10) dosed at 1000 mg/kg/day died on day 84, and histopathology showed hypertrophy of the centrilobular hepatocytes. In the survivors, excretion of fluorescent yellow urine was observed in all dose groups.

Clinical signs: Blood chemistry revealed an increase in GPT activity in the 300 (males) and 1000 (both sexes) mg/kg groups. In the 1000 mg/kg group, decrease in blood urea nitrogen, albumin, total protein (females) and A/G ratio (males) were observed.

Body weights: Suppressed body weight gain was observed in the high dose group (1000 mg/kg).

Food consumption: No treatment-related changes were observed in food consumption.

Hematology: In the 1000 mg/kg group, hematology and blood chemistry revealed decrease in RBC count, hemoglobin, HCT, BUN (-30%) and albumin (-6%), and increase in reticulocyte ratio and ALT activity (+104%) (Table 12).

Table 12. Summary of hematology in mice

Sex	Males			Females		
Dose (mg/kg/day)	100	300	1000	100	300	1000
No. of animals	10	10	9	10	10	10
RBC	N	N	-7%**	N	N	-11%**
Hb	N	N	-8%**	N	N	-13%**
Ht	N	N	-6%**	N	N	-10%**
MCV	N	N	+2%*	+1%*	+3%**	+1%*
MCHC	N	N	-2%**	N	-2%**	-3%**
Reticulocyte	N	N	+28%*	N	N	+56%**
Platelet	N	N	N	+9%*	N	N
Monocyte	N	N	+100%*	N	N	N

Figures in the table indicate percentage of change against the control mean.
N: No remarkable changes.
* (**): p<0.05 (0.01) (significantly different from the control group)

Blood Chemistry: Significant increase in GPT activity, and decrease in ALP activity, albumin, A/G ratio and blood urea nitrogen were observed (Table 13).

Table 13. Summary of blood chemistry

Sex	Males			Females		
Dose (mg/kg/day)	100	300	1000	100	300	1000
No. of animals	10	10	9	10	10	10
GPT (ALAT)	N	+27%**	+104%**	N	N	+19%*
AlP	N	N	-21%**	-15%*	-24%**	-39%**
TP	N	N	N	N	N	-7%**
Albumin	N	N	-6%**	N	N	-9%**
A/G	-13%**	N	-11%**	N	-9%*	N
T.cho	N	N	N	+12%*	+12%*	+22%*
BUN	N	N	-30%**	N	N	-22%**

* (**): p<0.05 (0.01) (significantly different from control)

Gross pathology: Gross pathology revealed dark discoloration and white foci in the liver in the 1000 mg/kg group.

Organ weights: Decreases in ovary and uterus weights in the 300 mg/kg (-11 and -38%) and 1000 mg/kg (-17 and -25%) groups and decreases in the spleen (-32% females) and kidneys (males) weights in the high dose group (1000 mg/kg) were observed.

Histopathology: Adequate battery: yes (√), no ( ); Peer review: yes (√), no ( ).

In the liver, hypertrophy of the centrilobular hepatocytes was observed in the 300 and 1000 mg/kg dose groups (+14 to +58%), and diffuse vacuolation of the hepatocytes was observed in the 1000 mg/kg group, which may implicate induction of drug metabolizing enzymes. In the duodenum, hypertrophy of the mucosal epithelium (both sexes) and erosion (one male) were observed in the 1000 mg/kg group. In the adrenal, decreased incidence of spindle cell hyperplasia (both sexes) and decreased X-zone (females) were observed in the 1000 mg/kg. In the kidney, decreased incidence of tubular vacuolation (males) was observed in the 300 and 1000 mg/kg groups. In the ovary and thymus, atrophy was observed in females in the 1000 mg/kg group.

Toxicokinetics: The AUC of the major human metabolite (R-106583) at the NOAEL was > 200-fold higher than that projected in human plasma levels (Table 14).

Table 14: Prasugrel metabolites in mice and anticipated maximal human exposure multiples

Species Dose	R-138727 AUC_{0-24} µg•h/mL	MOS[a]	R-106583 AUC_{0-24} µg•h/mL	MOS[a]	Prasugrel Dose mg/m²	MOS[a]
Human[b]						
10 mg/day	0.0545	–	0.299	–	7.4	–
Mouse[e]						
100 mg/kg, M	15.7	288	86.55	289	300	41
30 mg/kg, F	6.38	117	23.12	77	90	12

[a] AUC_{0-24} in animals at NOAEL/AUC_{0-24} in humans, [b] mean AUC_{0-last},
[e] Toxicokinetics determined on Month 18 at NOEL for hepatocellular adenoma.

Summary: In the mice, prasugrel administered orally by gavage for 3-months, caused suppression of body weight gain, anemia, increase GPT activity, increased liver weight and hypertrophy of the centrilobular hepatocytes. The low dose (100 mg/kg) did not cause overt toxicity, although increased liver weight was observed. The MTD was considered to be 300 mg/kg group in which the primary effects include suppression of body weight gain (16 and 28% in males and females, respectively), increased liver weight and hypertrophy of the centrilobular hepatocytes. The AUC of the major human metabolite (R-106583) at the NOAEL (100 mg/kg) was about 200-fold higher than that projected in human plasma levels (Section 2.6.7. Tabulated Summary: Table 40).

3- and 6-month repeat-dose in Fisher 344 rat:

Key findings: In the rat repeated oral administration of prasugrel for 3- and 6-months at doses ≥ 100 mg/kg/day was associated with increased liver weight, hepatocellular hypertrophy, hypertrophy of thyroid follicular epithelium and proliferation of smooth endoplasmic reticulum, changes consistent with microsomal enzyme induction. Tendency for anemia, increases in reticulocyte ratio, and platelet count, prolongation of prothrombin time and activated partial thromboplastin time were observed at doses > 100 mg/kg. The NOAEL for prasugrel in the rat was considered to be 30 mg/kg, which provides about 18-fold higher level of the human major metabolite (Section 2.6.7. Tabulated Summary, Table 41).

Study no.: APRC-147-013, TR 142-019
Conducting laboratory: [redacted]
Date of study initiation: March 2, 1995 **Report date:** Jun 15, 2000
GLP compliance: Yes, **QA report:** yes (√), no ( ) b(4)
Drug: Prasugrel
Doses: 10, 30, 100 and 300 mg/kg/day, Vehicle tragacanth 0.5%
Species/strain: F344/ [redacted] (Fisher) Rats
Number/sex/group: n=15/sex/dose group
Route: Oral gavage

Results:

Mortality: No death occurred in the high dose during the study period.

Clinical signs: Excretion of fluorescent yellow urine was seen at doses ≥ 30 mg/kg, which is considered to be due to excretion of the test article or its metabolites.

Body weights: Suppressed body weight gain accompanying with decreased food consumption was seen in ≥ 100 mg/kg groups.

Food consumption: In the 100 mg/kg group, food consumption was significantly lower than that of the control group from day 98 in males and from day 112 in females. In the high dose group (300 mg/kg), food consumption was significantly lower in both sexes than that of the control group.

Hematology: Increase in platelets in both sexes at doses 100 and 300 mg/kg, prolongation of prothrombin time in males at the 300 mg/kg dose, prolongation of activated partial thromboplastin time in males at the 100 mg/kg dose and in both sexes of the 300 mg/kg group and increase in fibrinogen levels in males of the 300 mg/kg group were observed. In males, decrease in hemoglobin (-3 and 7%) and mean corpuscular hemoglobin concentration (-1 and 2%), increase in platelet (8 and 24%), and elongation of APTT (19 and 46%) were seen in the 100 and 300 mg/kg groups. In females, decrease in RBC(-5 and 9%), Hb (-5 and 10%) and HCT (-4 and 8%), and increase in platelets (8 and 12%) were seen in the 100 and 300 mg/kg groups.

Clinical chemistry: Tendencies for anemia at doses ≥ 100 mg/kg, and an increase of reticulocyte ratio in female rats treated with 300 mg/kg were observed. Decrease in total cholesterol and triglycerides in males at doses ≥ 100 mg/kg, and slight decrease in serum potassium and chloride in females of the 300 mg/kg group were observed. Increase in total protein was seen in males at doses ≥ 100 mg/kg, and increase in albumin of the 300 mg/kg group, which are considered to be due to increased protein synthesis in the liver accompanying with the induction of drug metabolizing enzymes.

Urinalysis: Excretion of fluorescent yellow urine was seen in females in the 30 mg/kg group and both sexes at doses ≥ 100 mg/kg. Increase of urobilinogen was seen in both sexes at doses ≥ 100 mg/kg. Significant decrease in occult blood was seen in the 10 and 100 mg/kg groups.

Gross pathology: Increase in liver weight was seen in males of the 10 mg/kg group and in both sexes at doses ≥ 30 mg/kg, and macroscopic darkening of the liver in both sexes at doses ≥ 100 mg/kg.

Organ weights: Significant increase in absolute (7 to 19%) and relative weights (7 to 60%) was noted in females of the 30 mg/kg group and in both sexes of the 100 and 300 mg/kg groups, and increase in relative weight was seen in males of the 10 and 30 mg/kg group (4 and 7%). Evidence of enzyme induction included increased liver weight, hypertrophy and acidophilic cytoplasm of hepatocytes, hypertrophy of thyroid follicular epithelium, and proliferation of smooth endoplasmic reticulum in the 100 mg/kg group. Decrease thymus and prostate weight in doses ≥ 100 mg/kg group and decrease of uterine weight in the 300 mg/kg group were observed.

Histopathology: Adequate battery: yes (√), no ( ); Peer review: yes (√), no ( ).

Histopathological examination revealed hypertrophy of the hepatocytes at doses ≥ 30 mg/kg, which is consistent with drug metabolizing enzyme induction.

Toxicokinetics: The $AUC_{0\text{-}24}$ of the human major metabolite (R-106583) at the NOAEL is about 18-fold higher than that projected in human plasma levels (Table 15).

Table 15: Prasugrel metabolites in the rat and projected human plasma exposure multiples

Species Dose	R-138727 AUC_{0-24} µg•h/mL	MOS[a]	R-106583 AUC_{0-24} µg•h/mL	MOS[a]	Prasugrel Dose mg/m²	MOS[a]
Human[b]						
10 mg/day	0.0545	–	0.299	–	7.4	–
Rat[c]						
30 mg/kg, M	5.02	92	5.44	18	180	24
30 mg/kg, F	9.55	175	11.13	37	180	24
Rat[f]						
100 mg/kg, M	57.9	1062	22.17	74	600	81
100 mg/kg, F	58.9	1081	43.34	145	600	81

[a] AUC_{0-24} in animals at the NOAEL/AUC_{0-24} in humans, [b] mean AUC_{0-last}, [c] Toxicokinetics on Day 28 at NOAEL for chronic toxicity, [f] Toxicokinetics determined on Month 18 at NOEL.

Summary: In the rat, the main changes observed in 6-month repeated oral administration of prasugrel were the suppression of body weight gain and decrease of food consumption in both sexes of the 100 and 300 mg/kg groups. Decrease in hemoglobin, prolonged prothrombin and activated thromboplastin time, increase in platelets, liver weight, hepatocellular hypertrophy and proliferation of SER were observed at doses ≥ 100 mg/kg. The NOAEL of prasugrel in the rat is considered to be about 30 mg/kg, which affords about 18-fold higher exposure to the human major metabolite at prasugrel therapeutic dose of 10 mg/day (Section 2.6.7. Tabulated Summary: Table 41).

3- and 9-month repeat-dose in Beagle dog:

Key findings: In the dog repeated oral administration of prasugrel for 3- and 9-months at 20 mg/kg was associated with decrease platelet aggregation (by > 35%), increase in ALP levels (> 2-fold), hypertrophy of hepatocytes accompanied by ground glass appearance of the liver, and proliferation of smooth-surfaced endoplasmic reticulum which may be due to an activation of drug metabolizing enzymes. The NOAEL for prasugrel in the dog was 4 mg/kg/day, which affords about 1.5-fold higher exposure to the human major metabolite at prasugrel dose of 10 mg/day (Section 2.6.7. Tabulated Summary: Table 42).

Study no.: APRC-147-014, B-4096, TR 142-100

Conducting laboratory: [redacted] b(4)

Date of study initiation: Nov 13, 1998 **Report date:** June 15, 2000

GLP compliance: Yes, **QA report:** yes (√), no ( )

Drug: Prasugrel

Doses: 0.8, 4 and 20 mg/kg/day, Vehicle tragacanth 0.5%

Species/strain: Beagle dog

Number/sex/group: 4/sex/dose group

Route: Orally by capsule

Results:

Mortality: No deaths were recorded in both sexes of each experimental group including the control throughout the treatment and recovery periods.