

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-287

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22,287

SERIAL NUMBER: 000

DATE RECEIVED BY CENTER: December 28, 2007

DRUG NAME: Kapidex / Dexlansoprazole Delayed Release Capsule /
TAK-390

INTENDED CLINICAL POPULATION: Patients with gastroesophageal
reflux disease (GERD) and erosive esophagitis.

SPONSOR: TAP Pharmaceutical Products, Inc.
Lake Forest, IL

DOCUMENTS REVIEWED: EDR - Module 4

REVIEW DIVISION: Division of Gastroenterology Products
(HFD-180)

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Date of review submission to Division File System (DFS):
December 1, 2008

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Executive Summary

1. Recommendations

1.1 Recommendation on approvability

From a preclinical standpoint, approval of dexlansoprazole is recommended for the proposed indications.

1.2 Recommendation for nonclinical studies:

The sponsor should be asked to conduct studies with dexlansoprazole on platelet aggregation using human peripheral platelets.

1.3 Recommendation on labeling: The proposed labeling should be revised as recommended below.

8.1 Pregnancy

Pregnancy Category B.

A reproduction study has been conducted in rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately 9-fold the maximum recommended human dexlansoprazole dose (60 mg) based on body surface area [BSA]) and has revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole.

Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

2. Summary of nonclinical findings:

The major target organ of toxicity was the stomach identified in the 3-month repeat-dose toxicity study in rats and dogs. The results indicated that both dexlansoprazole and lansoprazole have similar toxicity profiles. Dexlansoprazole was not teratogenic in the segment II reproductive toxicity study in rabbits. Dexlansoprazole was positive in the Ames tests and in the *in vitro* chromosome aberration test using Chinese hamster lung cells.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,287

Review number: 01

Sequence number/date/type of submission:

000 / December 28, 2007

Information to sponsor: Yes (x) No ()

Reviewer name: Ke Zhang

Division name: Division of Gastroenterology Products

HFD #: 180

Review completion date: December 1, 2008

Drug: Kapidex Delayed Release Capsules

Generic name: Dexlansoprazole / R-(+)-Lansoprazole

Code name: TAK-390 / TAK-390MR

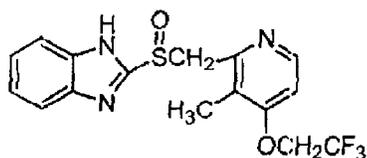
Chemical name:

R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl] benzimidazole

CAS registry number: 138530-94-6

Molecular formula/molecular weight: $C_{16}H_{14}F_3N_3O_2S$ and 369.36

Structure:



Relevant INDs/NDAs/DMFs: IND 69,927, NDA 20,406 (lansoprazole)

Drug class: Gastric parietal cell H^+/K^+ -ATPase inhibitor.

Indication: Dexlansoprazole is indicated for healing (b) (4) of all grades of erosive esophagitis (EE), maintaining healing of EE (b) (4), and treating

(b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (GERD).

Clinical formulation: Each capsule contains 30 mg, 60 mg (b) (4) of TAK-390. The clinical formulation is listed in the following tables.

Table 4 Quantitative Composition of Dexlansoprazole (b) (4) Granules (b) (4) (TAK-390MR Granules (b) (4) for 30 mg Capsules and Dexlansoprazole (b) (4) Granules (b) (4) (TAK-390MR Granules (b) (4) for 60 mg (b) (4) Capsules

Component	Quantity per Capsule (mg)		(b) (4)
	30 mg	60 mg	
(b) (4)	(b) (4)		
Sugar Spheres (500µm to 710µm)			
Magnesium Carbonate			
Sucrose			
Low-Substituted Hydroxypropyl Cellulose			
Hydroxypropyl Cellulose			
(b) (4)			
(b) (4)			
Hypromellose 2910			
Talc			
Titanium Dioxide			
(b) (4)			
(b) (4)			
Titanium Dioxide			
Talc			
Methacrylic Acid Copolymer (b) (4)			
Polyethylene Glycol 8000			
Polysorbate 80			
(b) (4)			
(b) (4)			
Colloidal Silicon Dioxide			
Talc			
SUB TOTAL	80	58	(b) (4)
(b) (4)			

Table 5 Quantitative Composition of Dexlansoprazole (b) (4) Granules (b) (4) (TAK-390MR Granules (b) (4)) for 30 mg, 60 mg (b) (4)

Component	Quantity per capsule (mg)		(b) (4)
	30 mg	60 mg	
(b) (4)	(b) (4)		
Sugar Spheres (500 µm to 710 µm)			
Magnesium Carbonate			
Sucrose			
Low-Substituted Hydroxypropyl Cellulose			
Hydroxypropyl Cellulose			
(b) (4)			
(b) (4)			
Hypromellose 2910			
Talc			
Titanium Dioxide			
(b) (4)			
(b) (4)			
Talc			
Methacrylic Acid Copolymer (b) (4)			
Methacrylic Acid Copolymer (b) (4)			
Triethyl Citrate			
(b) (4)			
(b) (4)			
(b) (4)			
Talc			
Colloidal Silicon Dioxide			
SUB TOTAL	105	210	(b) (4)
(b) (4)			

Route of administration: Oral capsules

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Any information or data necessary for approval of NDA 22,287 that TAP Pharmaceutical Products, Inc. does not own or has a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described

or referenced below from a previously approved application that TAP Pharmaceutical Products, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22,287.

Studies reviewed within this submission:

The Division and the sponsor agreed in the industry meeting on 06 October 2004 that the following nonclinical studies would support a NDA for dexlansoprazole: (1) In vitro Purkinje fiber study, (2) 3-month repeat-dose toxicity study in rats, (3) 3-month repeat-dose toxicity study in dogs, and (4) segment II reproductive toxicity study in rabbits. In addition, following genotoxicity studies were also conducted: Ames tests, an in vitro chromosomal aberration test using Chinese hamster lung cells, and an in vivo mouse micronucleus test based on the recommendation from the Division. Some of these studies were reviewed on March 8, 2005 and August 6, 2007 under IND 69,927 and the pharmacology reviews are incorporated into the current review.

Studies not reviewed within this submission: None.

PHARMACOLOGY

Brief summary

TAK-390 is the R-(+)-enantiomer of lansoprazole. TAK-390MR is a modified release formulation of TAK-390. The TAK-390MR dosage form releases drug over a prolonged period of time and produces lower plasma level of the active drug. Lansoprazole is a proton pump inhibitor and an approved drug for short-term treatment (up to 4 weeks) for healing and symptom relief of active duodenal ulcer. Lansoprazole is also indicated to maintain healing of duodenal ulcers.

In a published study in isolated canine parietal cells from gastric fundic mucosa (Biochemical Pharmacology, 42(10):1875-1878, 1991), both R-(+)- and S-(-)- enantiomers of lansoprazole inhibited the acid formations with IC50 of 59 μ M for R-(+)-enantiomer and 82 μ M for and S-(-)- enantiomer. In vivo pharmacology studies indicated that TAK-390 was more potent than

the racemic lansoprazole and T-168391 (S-(-)-lansoprazole) on the inhibition of basal gastric acid secretion with ID₅₀ of 1.2, 1.9, and 9.7 mg/kg for TAK-390, racemic lansoprazole, and T-168391, respectively in rats. TAK-390, racemic lansoprazole, and T-168391 also inhibited the histamine-stimulated acid secretion with ID₅₀ of 0.4, 0.8, and 4.0 mg/kg, respectively, in rats.

In an in vivo study in Heidenhain pouch dogs, TAK-390, racemic lansoprazole, and T-168391 inhibited the histamine-stimulated acid secretion with ID₅₀ of 0.06, 0.13, and 0.3 mg/kg, respectively. In the indomethacin-induced gastric mucosal lesions in rats, TAK-390, racemic lansoprazole, and T-168391 prevented the formation of the indomethacin-induced gastric mucosal lesions with ID₅₀ of 2.3, 7.6, and 16.5 mg/kg, respectively. In the mepiritole-induced duodenal mucosal lesions in rats, TAK-390, racemic lansoprazole, and T-168391 prevented the formation of the mucosal lesions with ID₅₀ of 0.2, 0.7, and 1.2 mg/kg, respectively. In a reflux esophagitis model in rats, TAK-390 and racemic lansoprazole inhibited the formation of the thoracic esophageal lesion induced by pylorus and forestomach ligation with ID₅₀ of 1.3 and 3.5 mg/kg, respectively, while T-168391 had no effects at doses up to 10 mg/kg. The results suggest that the pharmacological activity of racemic lansoprazole are mainly from its R-(+)-enantiomer, TAK-390.

2.6.2.4 Safety pharmacology

Cardiovascular effects:

In a study with isolated cardiac Purkinje fibers from dogs, the effects of TAK-390 on action potentials were evaluated at concentrations of 1, 10, and 100 µM. The Purkinje fibers were paced at 0.5 and 1 Hz. The results indicated that TAK-390 did not have any effects on action potential duration at 60% and 90% (APD60 and APD90), resting membrane potential (RMP), and upstroke amplitude at concentrations of 1-10 µM. At higher concentration (100 µM), TAK-390 shortened APD60 (~35%) and APD90 (~19%) and decreased the maximum rate of depolarization (20%). In contrast, the reference control, dl-Sotalol (50 µM), increased APD60 and APD90 by 45-67%. These effects were observed at both 0.5 and 1 Hz.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Pharmacokinetic studies demonstrated that TAK-390 was orally absorbed with oral bioavailability of 2.7% in rats and 22% in dogs. The maximum plasma concentration was achieved at 0.2 hours after oral dose in rats ($C_{max} = 22$ ng/ml) and dogs ($C_{max} = 442$ ng/ml). In contrast, the modified release formulation of TAK-390 was absorbed slowly with T_{max} of 1.3-1.6 hours in rats and 2.3 hours in dogs ($T_{max} = 0.3$ hours in rats and 1.3-1.7 hours in dogs for racemic lansoprazole). It declined quickly with plasma half life of 0.6 hours in both rats and dogs. A number of sulfone and sulfide metabolites were identified in the plasma following oral dose of TAK-390. These metabolites accounted for 1.1-32.4% in rats and 0.08-22.4% in dogs of the sample radioactivity. CYP2C19 and CYP3A4 were the major metabolic enzymes for biotransformation of TAK-390, lansoprazole, and T-168391.

2.6.4.3 Absorption

Following oral administration of radiolabeled TAK-390 (2 mg/kg ^{14}C -TAK-390), approximately 55% and 68% of the radioactivity was absorbed in rats and dogs, respectively (study# TAK-390-0000). The oral bioavailability of TAK-390 was 2.7% in rats and 22.0% in dogs. Maximum plasma concentrations were 22 ng/mL for rats and 442 ng/mL for dogs achieved at 0.2 hours after oral dose. The elimination half-life was 0.6 hours for both species. Another study indicated that TAK-390 was orally absorbed from most of the small and large intestines (study # TAK-390/00029). In mice, following oral gavage dose of TAK-390 at 1 g/kg the peak plasma level ($C_{max}=27583$ ng/ml) was reached at 1 hour after dosing and AUC₀₋₂₄ value was 80157 ng.h/ml (study # 07-44/tk).

2.6.4.4 Distribution

The radioactivity was rapidly distributed throughout the body after oral administration of 2 mg/kg [^{14}C]-TAK-390 to rats, with relatively high concentrations in the stomach, liver, intestine, kidney, and thyroid (study# TAK-390-0000). Beside the gastrointestinal tract and blood, high level of the radioactivity was also found in the eye (mainly in uveal tract) (study # 6764-376), suggesting that dexlansoprazole may bind to melanin. In vitro studies indicated that TAK-390 was bound

Table 23
Percent of sample radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to male rats (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Percent of Sample Radioactivity				
			Collection Time (Hours)				
			0.5	1	2	4	6
M3	2.50	Unknown	7.86	12.11	10.26	10.43	27.65
M8	5.50-6.00	Unknown	ND	ND	4.30	7.18	2.49
M9A	6.50-7.50	Unknown	ND	ND	2.77	13.18	8.60
M11	8.00	Unknown	ND	ND	5.45	ND	ND
M15	9.70	Unknown	0.77	ND	ND	ND	ND
M-XI	10.0-10.2	2-S-N-acetylcysteiny1 benzimidazole	ND	1.78	4.41	8.73	4.59
M19	10.7	Unknown	ND	1.34	ND	ND	ND
M20A	11.4-11.6	Unknown	1.03	4.68	13.77	5.38	ND
M21	12.3-12.5	Unknown	1.21	1.11	ND	6.22	5.49
M25A	13.5-14.0	Unknown	0.21	ND	ND	ND	3.69
M26	14.1-15.0	5-glucuronyloxy dexlansoprazole	0.56	ND	5.51	3.28	4.12
M30	16.2-16.3	Unknown	8.32	1.11	ND	ND	ND
M32	16.5-17.0	Unknown	5.88	1.63	4.69	2.94	ND
M33	17.1-17.4	5-glucuronyloxy dexlansoprazole sulfide	4.59	3.94	ND	ND	ND
M34	17.5-18.5	4-glucuronyloxy dexlansoprazole sulfide	13.15	8.69	9.75	11.62	14.78
M35	18.4-18.8	Hydroxysulfonyloxy dexlansoprazole	1.80	8.92	ND	ND	ND
M37A	19.5-20.1	Dihydroxy dexlansoprazole sulfone	ND	4.23	7.67	10.75	6.72
M38	20.2-21.0	5-sulfonyloxy dexlansoprazole sulfide	27.16	28.31	15.10	19.86	19.73
M39	21.4-22.1	4-sulfonyloxy dexlansoprazole sulfide	2.03	3.79	9.72	ND	ND
M42A	23.1	Unknown	1.33	ND	ND	ND	ND
Dexlansoprazole ^a	27.8-28.0	Parent	13.34	8.10	1.94	0.43	2.13
M-VII	30.8-31.0	Dexlansoprazole sulfone	5.53	3.34	1.56	ND	ND
M-I	35.4-35.5	Dexlansoprazole sulfide	3.54	5.20	2.35	ND	ND
		Total Identified in Chromatogram	71.1	76.3	52.5	51.4	48.0
		Total	98.3	98.3	99.3	100	100

ND Peak not detected or below the limit of quantitation (1.0% of run).
a Co-eluted with 5-hydroxy dexlansoprazole sulfide (M-IV). The presence of M-IV was confirmed by LC/MS analysis in some samples, primarily those at later time points. The percentage of M-IV increased over time.

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Table 24
Concentrations of radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to male rats (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Concentration (µg equivalents ¹⁴ C-Dexlansoprazole/g)				
			Collection Time (Hours)				
			0.5	1	2	4	6
M3	2.50	Unknown	0.181	0.130	0.0466	0.0420	0.0474
M8	5.50-6.00	Unknown	ND	ND	0.0195	0.0289	0.00427
M9A	6.50-7.50	Unknown	ND	ND	0.0126	0.0531	0.0147
M11	8.00	Unknown	ND	ND	0.0247	ND	ND
M15	9.70	Unknown	0.0178	ND	ND	ND	ND
M-XI	10.0-10.2	2-S-N-acetylcysteinyl benzimidazole	ND	0.0190	0.0200	0.0352	0.00786
M19	10.7	Unknown	ND	0.0143	ND	ND	ND
M20A	11.4-11.6	Unknown	0.0238	0.0500	0.0625	0.0217	ND
M21	12.3-12.5	Unknown	0.0279	0.0119	ND	0.0251	0.00940
M25A	13.3-14.0	Unknown	0.00485	ND	ND	ND	0.00632
M26	14.1-15.0	5-glucuronyloxy dexlansoprazole	0.0129	ND	0.0250	0.0132	0.00706
M30	16.2-16.3	Unknown	0.192	0.0119	ND	ND	ND
M32	16.5-17.0	Unknown	0.136	0.0174	0.0213	0.0118	ND
M33	17.1-17.4	5-glucuronyloxy dexlansoprazole sulfide	0.106	0.0421	ND	ND	ND
M34	17.5-18.5	4-glucuronyloxy dexlansoprazole sulfide	0.303	0.0929	0.0443	0.0468	0.0253
M35	18.4-18.8	Hydroxysulfonyloxy dexlansoprazole	0.0415	0.0954	ND	ND	ND
M37A	19.5-20.1	Dihydroxy dexlansoprazole sulfone	ND	0.0452	0.0348	0.0433	0.0115
M38	20.2-21.0	5-sulfonyloxy dexlansoprazole sulfide	0.627	0.303	0.0685	0.0800	0.0338
M39	21.4-22.1	4-sulfonyloxy dexlansoprazole sulfide	0.0469	0.0405	0.0441	ND	ND
M42A	23.1	Unknown	0.0307	ND	ND	ND	ND
Dexlansoprazole ^a	27.8-28.0	Parent	0.308	0.0866	0.00881	0.00173	0.00365
M-VII	30.8-31.0	Dexlansoprazole sulfone	0.128	0.0357	0.00708	ND	ND
M-I	35.4-35.5	Dexlansoprazole sulfide	0.0817	0.0556	0.0107	ND	ND
Total in Chromatogram			2.27	1.05	0.451	0.403	0.171
Total in Pooled Sample			2.45	1.17	0.571	0.463	0.226

ND Peak not detected or below the limit of quantitation (1.0% of run).
a Co-eluted with 5-hydroxy dexlansoprazole sulfide (M-IV). The presence of M-IV was confirmed by LC/MS analysis in some samples, primarily those at later time points. The percentage of M-IV increased over time.

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Table 25
Percent of sample radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after
administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to female rats (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Percent of Sample Radioactivity				
			Collection Time (Hours)				
			0.5	1	2	4	6
M3	2.50	Unknown	2.99	12.02	45.79	17.66	10.10
M9A	6.50-7.50	Unknown	ND	2.62	ND	4.08	7.05
M11	8.00	Unknown	ND	ND	ND	ND	3.94
M15	9.70	Unknown	2.67	ND	ND	ND	ND
M-XI	10.0-10.2	2-S- <i>N</i> -acetylcysteinyl benzimidazole	1.28	3.45	ND	2.46	ND
M19	10.7	Unknown	1.48	ND	ND	ND	ND
M20A	11.4-11.6	Unknown	1.64	1.73	6.96	ND	ND
M21	12.3-12.5	Unknown	0.40	2.67	8.42	13.74	10.07
M25A	13.3-14.0	Unknown	0.60	1.34	1.10	ND	3.21
M26	14.1-15.0	5-glucuronyloxy dexlansoprazole	0.28	1.22	ND	4.44	9.69
M32	16.5-17.0	Unknown	0.40	ND	8.06	32.91	ND
M33	17.1-17.4	5-glucuronyloxy dexlansoprazole sulfide	0.24	ND	1.10	ND	ND
M34	17.5-18.5	4-glucuronyloxy dexlansoprazole sulfide	0.08	2.95	1.10	ND	32.43
M35	18.4-18.8	Hydroxysulfonyloxy dexlansoprazole	3.03	ND	ND	ND	ND
M37A	19.5-20.1	Dihydroxy dexlansoprazole sulfone	ND	1.28	8.06	ND	ND
M38	20.2-21.0	5-sulfonyloxy dexlansoprazole sulfide	13.20	5.34	4.03	12.75	9.61
M39	21.4-22.1	4-sulfonyloxy dexlansoprazole sulfide	ND	ND	1.47	7.68	8.64
M42A	23.1	Unknown	0.36	ND	ND	ND	ND
Dexlansoprazole ^a	27.8-28.0	Parent	57.24	53.31	13.92	3.36	4.64
M-VII	30.8-31.0	Dexlansoprazole sulfone	4.35	5.68	ND	0.35	0.38
M-I	35.4-35.5	Dexlansoprazole sulfide	6.28	2.73	ND	ND	ND
		Total Identified in Chromatogram	85.7	74.7	29.7	26.6	55.7
		Total	96.5	96.3	100	99.4	99.8

ND Peak not detected or below the limit of quantitation (1.0% of run).

^a Co-eluted with 5-hydroxy dexlansoprazole sulfide (M-IV). The presence of M-IV was confirmed by LC/MS analysis in some samples, primarily those at later time points. The percentage of M-IV increased over time.

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Table 26
Concentrations of radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to female rats (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Concentration (µg equivalents ¹⁴ C-Dexlansoprazole/g)				
			Collection Time (Hours)				
			0.5	1	2	4	6
M3	2.50	Unknown	0.0499	0.149	0.167	0.0716	0.0185
M9A	6.50-7.50	Unknown	ND	0.0325	ND	0.0165	0.0129
M11	8.00	Unknown	ND	ND	ND	ND	0.00720
M15	9.70	Unknown	0.0446	ND	ND	ND	ND
M-XI	10.0-10.2	2-S- <i>N</i> -acetylcysteiny benzimidazole	0.0214	0.0428	ND	0.00997	ND
M19	10.7	Unknown	0.0247	ND	ND	ND	ND
M20A	11.4-11.6	Unknown	0.0274	0.0215	0.0254	ND	ND
M21	12.3-12.5	Unknown	0.00668	0.0331	0.0307	0.0557	0.0184
M25A	13.3-14.0	Unknown	0.0100	0.0166	0.00401	ND	0.00587
M26	14.1-15.0	5-glucuronyloxy dexlansoprazole	0.00467	0.0151	ND	0.0180	0.0177
M32	16.5-17.0	Unknown	0.00668	ND	0.0294	0.133	ND
M33	17.1-17.4	5-glucuronyloxy dexlansoprazole sulfide	0.00401	ND	0.00401	ND	ND
M34	17.5-18.5	4-glucuronyloxy dexlansoprazole sulfide	0.00134	0.0366	0.00401	ND	0.0593
M35	18.4-18.8	Hydroxysulfonyloxy dexlansoprazole	0.0506	ND	ND	ND	ND
M37A	19.5-20.1	Dihydroxy dexlansoprazole sulfone	ND	0.0159	0.0294	ND	ND
M38	20.2-21.0	5-sulfonyloxy dexlansoprazole sulfide	0.220	0.0663	0.0147	0.0517	0.0176
M39	21.4-22.1	4-sulfonyloxy dexlansoprazole sulfide	ND	ND	0.00536	0.0311	0.0158
M42A	23.1	Unknown	0.00601	ND	ND	ND	ND
Dexlansoprazole ^a	27.8-28.0	Parent	0.955	0.662	0.0508	0.0136	0.00848
M-VII	30.8-31.0	Dexlansoprazole sulfone	0.0726	0.0705	ND	0.00142	0.00069
M-I	35.4-35.5	Dexlansoprazole sulfide	0.105	0.0339	ND	ND	ND
Total in Chromatogram			1.61	1.20	0.365	0.403	0.182
Total in Pooled Sample			1.83	1.33	0.517	0.436	0.238

ND Peak not detected or below the limit of quantitation (1.0% of run).

a Co-eluted with 5-hydroxy dexlansoprazole sulfide (M-IV). The presence of M-IV was confirmed by LC/MS analysis in some samples, primarily those at later time points. The percentage of M-IV increased over time.

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Summary of identified metabolites in bile, urine, and feces in
bile duct-intact and bile duct-cannulated rats

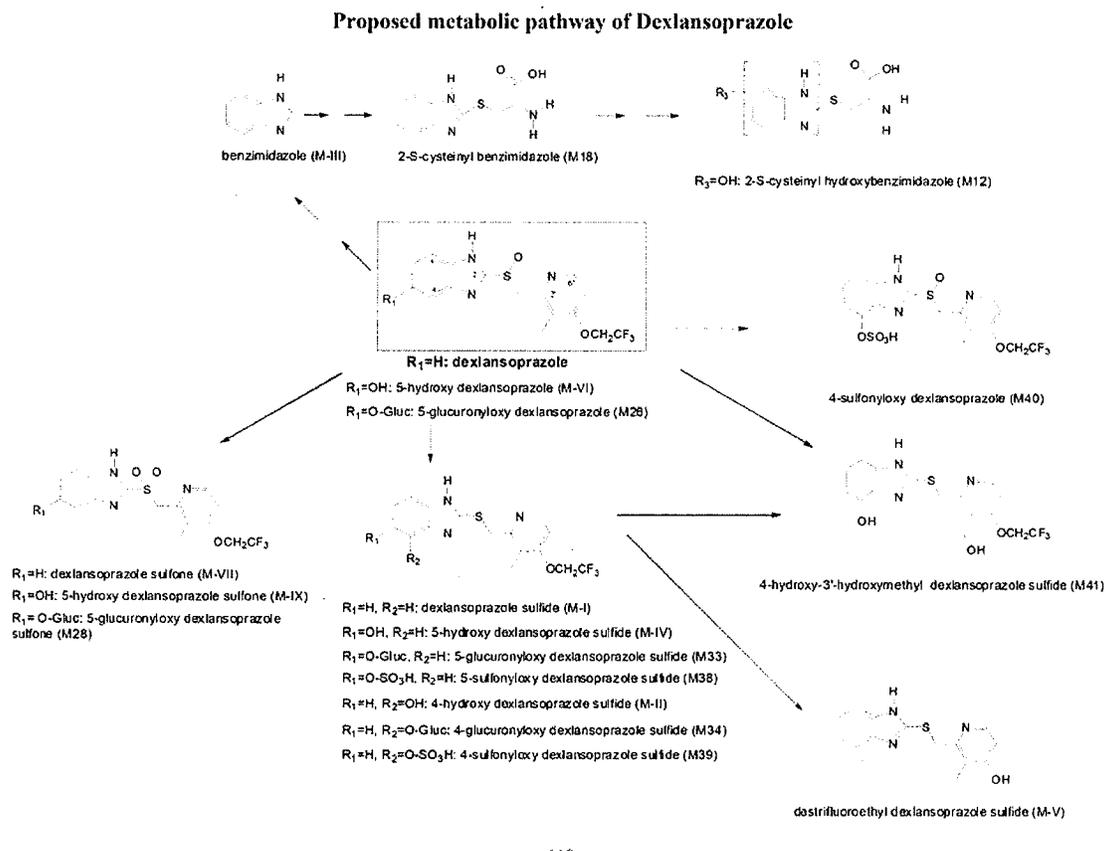
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Metabolite	Percent of Dose in Samples							
	Male				Female			
	Bile (0-8 hrs)	Urine (0-24 hrs)	Feces (0-48 hrs)	Total	Bile (0-8 hrs)	Urine (0-24 hrs)	Feces (0-48 hrs)	Total
Bile duct intact rats								
Mean percent of dose excreted	NA	23.2	68.7	91.9	NA	20.6	68.4	89.0
Dexlansoprazole	NA	ND	ND	0.00	NA	ND	ND	0.00
2-S-N-acetylcysteiny hydroxybenzimidazole (M9)	NA	4.61	ND	4.61	NA	3.08	ND	3.08
2-S-N-acetylcysteiny benzimidazole (M-XI)	NA	4.27	ND	4.27	NA	4.32	ND	4.32
Benzimidazole (M-III)	NA	1.52	ND	1.52	NA	1.05	ND	1.05
5-glucuronyloxy dexlansoprazole sulfide (M33)	NA	0.39	ND	0.39	NA	2.82	ND	2.82
5-hydroxy-3'-hydroxymethyl dexlansoprazole sulfide (M37)	NA	ND	2.95	2.95	NA	ND	3.07	3.07
5-sulfonyloxy-dexlansoprazole sulfide (M38)	NA	2.58	ND	2.58	NA	1.21	ND	1.21
4-hydroxy-3'-hydroxymethyl dexlansoprazole sulfide (M41)	NA	ND	2.64	2.64	NA	ND	2.16	2.16
5-hydroxy dexlansoprazole sulfone (M-IX)	NA	ND	2.37	2.37	NA	0.19	1.20	0.39
5-hydroxy dexlansoprazole sulfide (M-IV)	NA	0.23	20.5	20.7	NA	1.97	23.4	25.4
4-hydroxy dexlansoprazole sulfide (M-II)	NA	ND	1.69	1.69	NA	ND	2.46	2.46
Total identified in pooled sample	NA	13.6	30.2	43.7	NA	14.6	32.3	46.0
% of the total dose identified	NA	58.6	44.0	NA	NA	70.9	47.2	NA
Bile duct-cannulated rats								
Mean percent of dose excreted	49.3	NA	NA	49.3	49.6	NA	NA	49.6
Dexlansoprazole	ND	NA	NA	ND	ND	NA	NA	ND
2-S-glycinylcysteiny benzimidazole (M10)	0.39	NA	NA	0.39	0.53	NA	NA	0.53
2-S-N-acetylcysteiny benzimidazole (M-XI)	0.53	NA	NA	0.53	0.12	NA	NA	0.12
Destrifluoroethyl dexlansoprazole sulfide (M-V)	2.09	NA	NA	2.09	1.35	NA	NA	1.35
5-glucuronyloxy dexlansoprazole (M26)	8.92	NA	NA	8.92	9.10	NA	NA	9.10
3'-glucuronyloxymethyl dexlansoprazole sulfide (M27)	0.53	NA	NA	0.53	0.81	NA	NA	0.81
5-glucuronyloxy dexlansoprazole sulfone (M28)	1.57	NA	NA	1.57	0.05	NA	NA	0.05
5-glucuronyloxy dexlansoprazole sulfide (M33)	7.04	NA	NA	7.04	5.01	NA	NA	5.01
4-glucuronyloxy dexlansoprazole sulfide (M34)	1.35	NA	NA	1.35	1.60	NA	NA	1.60
5-sulfonyloxy dexlansoprazole sulfide (M38)	11.1	NA	NA	11.1	14.4	NA	NA	14.4
4-sulfonyloxy dexlansoprazole sulfide (M39)	1.00	NA	NA	1.00	1.11	NA	NA	1.11
5-hydroxy dexlansoprazole sulfide (M-IV)	0.25	NA	NA	0.25	2.20	NA	NA	2.20
Total identified in pooled sample	34.8	NA	NA	34.8	36.3	NA	NA	36.3
% of the total dose identified	70.6	NA	NA	NA	73.2	NA	NA	NA

NA Not applicable.

ND Not detected.

The proposed metabolic pathway in dogs is depicted in the following table (study 6764-374).



The metabolites identified in dogs were summarized in the following tables.

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Table 13
Percent of sample radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to male bile duct-intact dogs (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Percent of Sample Radioactivity								
			Collection Time (Hours)								
			0.5	1	2	3	4	6	8	12	24
M1	1.83	Unknown	ND	1.20	2.58	3.86	4.80	5.51	6.24	4.44	ND
M2	2.33-2.50	Unknown	ND	0.08	0.15	0.21	0.39	0.37	0.46	0.53	ND
M4	3.33	Unknown	ND	ND	ND	ND	ND	ND	ND	ND	25.87
M6	3.67	Unknown	ND	ND	0.16	0.06	ND	ND	ND	ND	41.75
M7	4.50-4.83	Unknown	ND	0.24	ND	0.84	0.63	3.01	1.19	ND	7.35
M8	5.00	Unknown	ND	ND	0.59	0.82	1.41	ND	ND	ND	ND
M9A	5.33	Unknown	ND	ND	0.49	0.67	1.03	ND	0.73	0.53	3.47
M10A	5.50-5.67	Unknown	ND	0.45	ND	0.65	1.99	ND	1.83	0.88	ND
M11	6.00-6.17	Unknown	ND	0.25	0.48	ND	ND	1.78	ND	ND	1.73
M12A	6.33-6.67	Unknown	ND	ND	0.43	1.43	2.49	1.34	2.75	1.05	ND
M13	6.83-7.17	Unknown	ND	0.52	0.51	1.01	1.55	0.89	1.28	0.53	ND
M16	8.50	Unknown	ND	0.39	ND	ND	ND	ND	0.27	ND	ND
M17	8.83-9.83	Unknown	ND	0.70	0.92	1.50	0.65	0.22	ND	ND	ND
M20	10.33-10.67	Unknown	ND	ND	2.22	2.59	4.51	6.40	4.95	ND	ND
M22	10.83-11.00	Unknown	ND	3.47	3.29	4.89	5.01	6.12	5.97	ND	ND
M23	11.17-11.33	Unknown	ND	ND	1.51	2.61	ND	6.73	ND	9.39	ND
M24	11.50-11.83	Unknown	ND	1.26	ND	ND	3.55	ND	6.42	7.27	ND
M26A	12.00-12.33	Unknown	ND	ND	ND	ND	ND	5.12	4.86	ND	ND
M26	12.50-12.83	5-glucuronidoxylansoprazole	1.28	7.40	12.06	10.80	9.18	1.50	ND	ND	ND
M28	13.00-13.33	5-glucuronidoxylansoprazole sulfide	1.38	5.71	7.55	10.16	9.18	11.20	12.58	5.85	ND
M29	13.50-13.67	Unknown	ND	ND	2.50	3.35	4.57	7.88	9.00	ND	ND
M30	13.83-14.00	Unknown	ND	ND	3.36	6.08	11.19	16.16	13.14	ND	ND
M31	14.17-14.67	Unknown	ND	2.45	1.92	2.84	2.80	2.34	2.38	36.55	ND
M34A	14.83-15.17	Unknown	ND	1.30	0.11	ND	ND	ND	ND	2.66	ND
M34A	15.83	Unknown	ND	ND	0.48	ND	ND	0.22	ND	ND	6.03
M35A	16.33-16.50	Unknown	ND	ND	0.62	1.35	ND	1.71	1.01	ND	ND
M33	16.67-17.17	5-glucuronidoxylansoprazole sulfide	ND	0.93	ND	ND	1.73	1.84	ND	0.53	ND
M34	17.33-17.83	4-glucuronidoxylansoprazole sulfide	ND	1.27	1.75	2.58	3.92	ND	0.46	ND	ND
M38	19.67-20.33	5-sulfonyloxylansoprazole sulfide	ND	0.83	0.77	1.56	3.71	13.85	17.17	22.36	ND
M44	20.83-21.83	Unknown	ND	0.67	0.43	0.57	1.62	3.99	2.66	1.24	ND
Dexlansoprazole	26.00-27.20	Parent	\$6.88	53.80	35.09	19.93	6.70	ND	ND	ND	1.73
M-VII	29.50-30.50	Dexlansoprazole sulfone	10.45	13.96	17.51	18.24	15.45	ND	ND	ND	12.07
M-I	34.83	Dexlansoprazole sulfide	ND	1.54	0.42	0.09	ND	ND	ND	ND	ND
Total Identified in Chromatogram			100	85.5	75.2	63.4	49.9	38.4	30.2	28.7	13.8
Total			100.0	98.4	97.9	98.7	98.0	98.2	95.3	93.8	100

ND Peak not detected or below the limit of quantitation (1.0% of run).

Note: If a metabolite was detected in one sample ≥1% of the radioactivity and <1% of the radioactivity in remaining samples, that metabolite was reported for consistency.

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Table 14
Concentrations of radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to male bile duct-intact dogs (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Concentration (µg equivalents ¹⁴ C-Dexlansoprazole/g)								
			Collection Time (Hours)								
			0.5	1	2	3	4	6	8	12	24
M1	1.83	Unknown	ND	0.0611	0.0844	0.0674	0.0473	0.0153	0.0289	0.0131	ND
M2	2.33-2.50	Unknown	ND	0.00394	0.00490	0.00371	0.00389	0.00235	0.00211	0.00156	ND
M4	3.33	Unknown	ND	ND	ND	ND	ND	ND	ND	ND	0.0114
M6	3.67	Unknown	ND	ND	0.00538	0.00113	ND	ND	ND	ND	0.0184
M7	4.50-4.83	Unknown	ND	0.0121	ND	0.0147	0.00619	0.0192	0.00549	ND	0.00324
M8	5.00	Unknown	ND	ND	0.0193	0.0143	0.0139	ND	ND	ND	ND
M9A	5.33	Unknown	ND	ND	0.0161	0.0117	0.0102	ND	0.00337	0.00156	0.00153
M10A	5.50-5.67	Unknown	ND	0.0226	ND	0.0114	0.0196	ND	0.00845	0.00261	ND
M11	6.00-6.17	Unknown	ND	0.0125	0.0158	ND	ND	0.0114	ND	ND	0.00076
M12A	6.33-6.67	Unknown	ND	ND	0.0142	0.0249	0.0245	0.00860	0.0127	0.00311	ND
M13	6.83-7.17	Unknown	ND	0.0266	0.0168	0.0176	0.0153	0.00568	0.00593	0.00156	ND
M16	8.50	Unknown	ND	0.0197	ND	ND	ND	ND	0.00126	ND	ND
M17	8.83-9.83	Unknown	ND	0.0354	0.0300	0.0261	0.00639	0.00138	ND	ND	ND
M20	10.33-10.67	Unknown	ND	ND	0.0728	0.0453	0.0445	0.0410	0.0229	ND	ND
M22	10.83-11.00	Unknown	ND	0.176	0.108	0.0853	0.0494	0.0392	0.0276	ND	ND
M23	11.17-11.33	Unknown	ND	ND	0.0495	0.0456	ND	0.0431	ND	0.0277	ND
M24	11.50-11.83	Unknown	ND	0.6639	ND	ND	0.0350	ND	0.0297	0.0215	ND
M26A	12.00-12.33	Unknown	ND	ND	ND	ND	ND	0.0328	0.0225	ND	ND
M26	12.50-12.83	5-glucuronoyloxy dexlansoprazole	0.0590	0.376	0.393	0.188	0.0905	0.00957	ND	ND	ND
M28	13.00-13.33	5-glucuronoyloxy dexlansoprazole sulfone	0.0636	0.291	0.248	0.177	0.0906	0.0717	0.0582	0.0173	ND
M29	13.50-13.67	Unknown	ND	ND	0.0818	0.0590	0.0451	0.0504	0.0416	ND	ND
M30	13.83-14.00	Unknown	ND	ND	0.110	0.106	0.110	0.103	0.0608	ND	ND
M31	14.17-14.67	Unknown	ND	0.124	0.0628	0.0496	0.0276	0.0150	0.0110	0.108	ND
M33A	14.83-15.17	Unknown	ND	0.0661	0.00351	ND	ND	ND	ND	0.00785	ND
M34A	15.83	Unknown	ND	ND	0.0158	ND	ND	0.00138	ND	ND	0.00266
M35A	16.33-16.50	Unknown	ND	ND	0.0202	0.0236	ND	0.0110	0.00466	ND	ND
M33	16.67-17.17	5-glucuronoyloxy dexlansoprazole sulfide	ND	0.0472	ND	ND	0.0171	0.0118	ND	0.00156	ND
M34	17.33-17.83	4-glucuronoyloxy dexlansoprazole sulfide	ND	0.0644	0.0573	0.0449	0.0387	ND	0.00211	ND	ND
M38	19.67-20.33	5-sulfonoyloxy dexlansoprazole sulfide	ND	0.0420	0.0251	0.0271	0.0366	0.0887	0.0794	0.0660	ND
M44	20.83-21.83	Unknown	ND	0.0339	0.0142	0.01000	0.0160	0.0256	0.0123	0.00366	ND
Dexlansoprazole	26.00-27.20	Parent	4.00	2.73	1.15	0.348	0.0661	ND	ND	ND	0.00076
M-VII	29.50-30.50	Dexlansoprazole sulfone	0.482	0.709	0.574	0.318	0.152	ND	ND	ND	0.00532
M-I	34.83	Dexlansoprazole sulfide	ND	0.0781	0.0137	0.00153	ND	ND	ND	ND	ND
Total in Chromatogram			4.61	5.00	3.21	1.72	0.967	0.628	0.441	0.277	0.0441
Total in Pooled Sample			4.83	5.24	3.78	2.04	1.2	0.772	0.579	0.381	0.15

ND Peak not detected or below the limit of quantitation (1.0% of run).

Note: If a metabolite was detected in one sample ≥1% of the radioactivity and <1% of the radioactivity in remaining samples, that metabolite was reported for consistency.

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Table 15
Percent of sample radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to female bile duct-intact dogs (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Percent of Sample Radioactivity									
			Collection Time (Hours)									
			0.5	1	2	3	4	6	8	12	24	
M1	1.83	Unknown	ND	2.12	5.57	4.86	6.03	7.03	11.29	10.81	12.72	
M2	2.35-2.50	Unknown	ND	0.29	0.66	0.38	0.76	0.37	1.61	1.19	0.70	
M4	3.33	Unknown	ND	ND	ND	ND	0.06	ND	ND	0.13	ND	
M7	4.50-4.83	Unknown	ND	0.47	1.11	0.40	ND	2.29	0.32	ND	ND	
M8	5.00	Unknown	ND	ND	1.01	0.68	ND	0.96	ND	ND	ND	
M9A	5.33	Unknown	ND	ND	ND	ND	ND	ND	ND	0.33	ND	
M10A	5.50-5.67	Unknown	ND	ND	1.97	0.86	2.57	2.16	0.32	ND	ND	
M11	6.00-6.17	Unknown	ND	ND	ND	ND	2.77	1.50	0.64	ND	ND	
M12A	6.33-6.67	Unknown	ND	0.97	1.62	1.19	ND	4.27	0.98	ND	ND	
M13	6.83-7.17	Unknown	ND	0.46	0.91	0.70	2.77	ND	0.83	1.45	ND	
M16	8.50	Unknown	ND	ND	ND	ND	0.70	ND	1.90	2.43	ND	
M17	8.83-9.83	Unknown	ND	0.55	0.58	0.72	1.10	0.62	6.55	2.56	4.69	
M19	10.00	Unknown	ND	ND	ND	ND	ND	ND	ND	6.69	3.29	
M20	10.33-10.67	Unknown	ND	ND	ND	ND	ND	5.01	3.21	5.05	3.74	
M22	10.83-11.00	Unknown	ND	5.38	8.40	6.79	ND	5.30	2.25	2.43	ND	
M23	11.17-11.33	Unknown	ND	1.59	ND	ND	9.35	4.95	2.92	5.57	6.12	
M24	11.50-11.83	Unknown	ND	ND	3.58	2.98	8.04	ND	7.95	7.61	3.29	
M26A	12.00-12.33	Unknown	ND	ND	ND	ND	ND	3.59	5.21	4.20	ND	
M26	12.50-12.83	5-glucuronoyloxy dexlansoprazole	ND	11.54	10.94	12.86	ND	3.05	ND	4.79	22.83	
M28	13.00-13.33	5-glucuronoyloxy dexlansoprazole sulfone	ND	13.66	11.13	14.75	8.16	8.63	16.06	8.59	ND	
M29	13.50-13.67	Unknown	ND	ND	4.14	ND	9.59	6.43	ND	ND	ND	
M30	13.83-14.00	Unknown	6.94	3.80	9.87	10.31	6.06	12.31	10.51	14.42	36.53	
M31	14.17-14.67	Unknown	ND	2.32	ND	3.94	15.92	3.35	1.87	ND	ND	
M33A	14.83-15.17	Unknown	ND	0.08	2.93	ND	2.77	ND	ND	0.13	ND	
M35A	16.33-16.50	Unknown	ND	1.23	ND	1.41	ND	2.36	1.83	0.66	ND	
M33	16.67-17.17	5-glucuronoyloxy dexlansoprazole sulfide	ND	ND	2.31	ND	2.99	1.69	ND	0.46	0.70	
M34	17.33-17.83	4-glucuronoyloxy dexlansoprazole sulfide	ND	1.76	2.67	1.87	1.46	1.20	0.90	0.73	ND	
M38A	18.17	Unknown	ND	ND	ND	ND	1.30	0.07	ND	ND	ND	
M38	19.67-20.33	5-sulfonyloxy dexlansoprazole sulfide	ND	0.91	2.59	1.69	5.48	16.02	16.16	16.86	3.99	
M44	20.83-21.83	Unknown	ND	0.26	2.19	0.81	6.00	3.82	4.04	2.10	ND	
Dexlansoprazole	26.00-27.20	Parent	80.67	36.20	12.43	18.46	0.58	ND	ND	ND	ND	
M-VII	29.50-30.50	Dexlansoprazole sulfone	8.61	12.35	11.31	11.84	3.60	1.09	ND	ND	ND	
M-I	34.83	Dexlansoprazole sulfide	ND	ND	0.08	0.08	ND	ND	ND	ND	ND	
Total Identified in Chromatogram			89.3	76.5	53.5	61.6	22.3	31.7	33.1	31.4	27.5	
Total			96.2	96.0	98.0	97.6	98.2	98.1	97.3	99.2	98.6	

ND Peak not detected or below the limit of quantitation (1.0% of run).

Note: If a metabolite was detected in one sample ≥1% of the radioactivity and <1% of the radioactivity in remaining samples, that metabolite was reported for consistency.

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Table 16
Concentrations of radioactivity as ¹⁴C-Dexlansoprazole or metabolites of ¹⁴C-Dexlansoprazole in pooled plasma after administration of a single oral dose of ¹⁴C-Dexlansoprazole (5 mg/kg) to female bile duct-intact dogs (Group 1)

Peak Identification	Retention Time (Minutes)	Proposed Identification	Concentration (µg equivalents ¹⁴ C-Dexlansoprazole/g)								
			Collection Time (Hours)								
			0.5	1	2	3	4	6	8	12	24
M1	1.83	Unknown	ND	0.0698	0.0873	0.0966	0.0545	0.0394	0.0493	0.0259	0.00996
M2	2.33-2.50	Unknown	ND	0.00959	0.0103	0.00762	0.00689	0.00206	0.00702	0.00284	0.00055
M4	3.33	Unknown	ND	ND	ND	ND	0.00056	ND	ND	0.00032	ND
M7	4.50-4.83	Unknown	ND	0.0156	0.0173	0.00792	ND	0.0128	0.00138	ND	ND
M8	5.00	Unknown	ND	ND	0.0158	0.0135	ND	0.00538	ND	ND	ND
M9A	5.33	Unknown	ND	ND	ND	ND	ND	ND	ND	0.00079	ND
M10A	5.50-5.67	Unknown	ND	ND	0.0309	0.0171	0.0232	0.0121	0.00138	ND	ND
M11	6.00-6.17	Unknown	ND	ND	ND	ND	0.0251	0.00841	0.00284	ND	ND
M12A	6.33-6.67	Unknown	ND	0.0317	0.0254	0.0237	ND	0.0239	0.00429	ND	ND
M13	6.83-7.17	Unknown	ND	0.0152	0.0143	0.0139	0.0251	ND	0.00362	0.00347	ND
M16	8.50	Unknown	ND	ND	ND	ND	0.00636	ND	0.00829	0.00583	ND
M17	8.83-9.83	Unknown	ND	0.0181	0.00905	0.0142	0.00995	0.00345	0.0286	0.00613	0.00367
M19	10.00	Unknown	ND	ND	ND	ND	ND	ND	ND	0.0160	0.00257
M20	10.33-10.67	Unknown	ND	ND	ND	ND	ND	0.0281	0.0140	0.0121	0.00293
M22	10.83-11.00	Unknown	ND	0.176	0.132	0.135	ND	0.0297	0.00982	0.00581	ND
M23	11.17-11.33	Unknown	ND	0.0524	ND	ND	0.0845	0.0277	0.0127	0.0133	0.00479
M24	11.50-11.83	Unknown	ND	ND	0.0562	0.0593	0.0727	ND	0.0347	0.0182	0.00257
M26A	12.09-12.33	Unknown	ND	ND	ND	ND	ND	0.0201	0.0227	0.0100	ND
M26	12.50-12.83	5-glucuronoyloxy dexlansoprazole	ND	0.379	0.172	0.256	ND	0.0170	ND	0.0115	0.0179
M28	13.00-13.33	5-glucuronoyloxy dexlansoprazole sulfide	ND	0.449	0.175	0.293	0.0737	0.0483	0.0701	0.0206	ND
M29	13.50-13.67	Unknown	ND	ND	0.0650	ND	0.0867	0.0360	ND	ND	ND
M30	13.83-14.00	Unknown	0.222	0.125	0.155	0.205	0.0547	0.0689	0.0459	0.0345	0.0286
M31	14.17-14.67	Unknown	ND	0.0761	ND	0.0783	0.144	0.0187	0.00818	ND	ND
M35A	14.83-15.17	Unknown	ND	0.00253	0.0459	ND	0.0250	ND	ND	0.00032	ND
M35A	16.33-16.50	Unknown	ND	0.0404	ND	0.0280	ND	0.0132	0.00799	0.00158	ND
M33	16.67-17.17	5-glucuronoyloxy dexlansoprazole sulfide	ND	ND	0.0362	ND	0.0270	0.00944	ND	0.00111	0.00055
M34	17.33-17.83	4-glucuronoyloxy dexlansoprazole sulfide	ND	0.0578	0.0419	0.0371	0.0132	0.00671	0.00392	0.00174	ND
M38A	18.17	Unknown	ND	ND	ND	ND	0.0127	0.00036	ND	ND	ND
M48	19.67-20.33	5-sulfonyloxy dexlansoprazole sulfide	ND	0.0308	0.0407	0.0336	0.0496	0.0896	0.0705	0.0403	0.00312
M44	20.83-21.83	Unknown	ND	0.00849	0.0344	0.0162	0.0542	0.0214	0.0176	0.00504	ND
Dexlansoprazole	26.00-27.20	Parent	2.58	1.19	0.195	0.367	0.00527	ND	ND	ND	ND
M-VII	29.50-30.50	Dexlansoprazole sulfone	0.276	0.405	0.177	0.235	0.0325	0.00611	ND	ND	ND
M-I	34.83	Dexlansoprazole sulfide	ND	ND	0.00126	0.00167	ND	ND	ND	ND	ND
		Total in Chromatogram	3.08	3.15	1.54	1.94	0.887	0.549	0.425	0.237	0.0772
		Total in Pooled Sample	3.5	3.47	1.77	2.32	0.983	0.685	0.589	0.393	0.156

ND Peak not detected or below the limit of quantitation (1.0% of run).

Note: If a metabolite was detected in one sample ≥1% of the radioactivity and <1% of the radioactivity in remaining samples, that metabolite was reported for consistency.

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Summary of identified metabolites in urine and feces of bile duct-intact dogs.

Metabolite	Percent of Dose in Samples					
	Male			Female		
	Urine (0-48 hrs)	Feces (0-72 hrs)	Total	Urine (0-48 hrs)	Feces (0-72 hrs)	Total
Bile duct-intact dogs (Group 1)						
Mean percent of dose excreted	28.5	52.0	80.5	27.4	57.4	84.8
Dexlansoprazole	ND	ND	ND	ND	ND	
2-S-cysteinyl hydroxybenzimidazole (M12)	3.69	ND	3.69	0.56	ND	0.56
2-S-cysteinyl benzimidazole (M18)	1.91	ND	1.91	0.99	ND	0.99
Benzimidazole (M-III)	0.82	ND	0.82	0.77	ND	0.77
5-glucuronyloxy dexlansoprazole (M26)	0.18	ND	0.18	1.64	ND	1.64
5-glucuronyloxy dexlansoprazole sulfone (M28)	1.61	ND	1.61	0.27	ND	0.27
5-glucuronyloxy dexlansoprazole sulfide (M33)	4.37	ND	4.37	4.73	ND	4.73
4-sulfonyloxy dexlansoprazole sulfide (M39)	0.37	ND	0.37	0.17	ND	0.17
4-sulfonyloxy dexlansoprazole (M40)	0.38	ND	0.38	0.14	ND	0.14
5-hydroxy dexlansoprazole (M-VI)	1.23	ND	1.23	1.84	ND	1.84
4-hydroxy-3'-hydroxymethyl dexlansoprazole sulfide (M41)	ND	1.06	1.06	ND	1.26	1.26
5-hydroxy dexlansoprazole sulfone (M-IX)	ND	0.92	0.92	ND	3.46	3.46
5-hydroxy dexlansoprazole sulfide (M-IV)	ND	16.3	16.3	0.02	20.0	20.02
4-hydroxy dexlansoprazole sulfide (M-II)	ND	7.63	7.63	ND	11.1	11.1
Dexlansoprazole sulfide (M-I)	ND	0.1	0.10	ND	0.05	0.05
Total identified in pooled sample	14.6	26.0	40.6	11.1	35.9	47.0
% of the total dose identified	51.2	50.0	NA	40.5	62.5	NA

hrs hours.
 NA Not applicable.
 ND Not detected.

Appears This Way On Original

Summary of identified metabolites in bile, urine, and feces of bile duct-cannulated dogs.

Metabolite	Percent of Dose in Samples							
	Male				Female			
	Bile (0-24 hrs)	Urine (0-48 hrs)	Feces (0-72 hrs)	Total	Bile (0-24 hrs)	Urine (0-48 hrs)	Feces (0-72 hrs)	Total
Bile duct-cannulated dogs (Group 2)								
Mean percent of dose excreted	44.5	22.3	22.6	89.4	62.4	21.4	4.37	88.2
Dexlansoprazole	ND	ND	ND	ND	ND	ND	ND	ND
2-S-cysteinyloxy hydroxybenzimidazole (M12)	ND	1.46	ND	1.46	ND	1.17	ND	1.17
2-S-cysteinyloxy benzimidazole (M18)	ND	1.86	ND	1.86	ND	2.42	ND	2.42
Benzimidazole (M-III)	ND	1.22	ND	1.22	ND	1.24	ND	1.24
5-glucuronyloxy dexlansoprazole (M26)	11.1	0.95	ND	12.1	23.0	1.10	ND	24.1
5-glucuronyloxy dexlansoprazole sulfone (M28)	6.74	0.94	ND	7.68	15.2	1.04	ND	16.2
5-glucuronyloxy dexlansoprazole sulfide (M33)	6.40	3.88	ND	10.3	4.27	3.90	ND	8.17
4-glucuronyloxy dexlansoprazole sulfide (M34)	6.02	ND	ND	6.02	8.93	ND	ND	8.93
5-sulfonyloxy dexlansoprazole sulfide (M38)	6.14	ND	ND	6.14	1.52	ND	ND	1.52
4-sulfonyloxy dexlansoprazole (M40)	2.41	0.05	ND	2.46	1.21	0.02	ND	1.23
5-hydroxy dexlansoprazole (M-VI)	ND	0.49	ND	0.49	ND	0.48	ND	0.48
4-hydroxy-3'-hydroxymethyl dexlansoprazole sulfide (M41)	ND	ND	0.45	0.45	ND	ND	ND	ND
5-hydroxy dexlansoprazole sulfone (MIX)	ND	ND	0.05	0.05	ND	ND	0.02	0.02
5-hydroxy dexlansoprazole sulfide (M-IV)	ND	ND	0.38	0.38	ND	0.02	0.16	0.18
4-hydroxy dexlansoprazole sulfide (M-II)	ND	ND	0.71	0.71	ND	ND	0.41	0.41
Dexlansoprazole sulfide (M-I)	ND	ND	0.63	0.63	ND	ND	0.09	0.09
Total identified in pooled sample	38.8	10.9	2.22	51.9	54.1	11.4	0.68	66.2
% of the total dose identified	87.2	48.9	9.82	NA	86.7	53.3	15.6	NA

hrs hours.
 NA Not applicable.
 ND Not detected.

In vitro studies with hepatic microsomes from rats, mice, dogs and humans show that there were no metabolites of TAK-390 specific for humans. The main metabolites produced by human microsomes were 5'-hydroxylation and sulfoxidation products. CYP2C19 and CYP3A4 were identified as the major metabolic enzymes involved in the biotransformation of TAK-390, T-168391, and lansoprazole using microsomes expressing the human CYP-isoforms and individual human hepatic microsomes.

The biotransformation from TAK-390 to T-168391 is minimal in both rats and dogs. However, when racemic lansoprazole (15, 50 or 150 mg/kg) was administered to rats and dogs, the C_{max} and AUC values for TAK-390 were much greater than those for T-168391.

The inhibitory effect of TAK-390 or T-168391 (1, 10, and 100 µmol/L) on CYP-specific enzyme activities was investigated using microsomes expressing the human CYP isoforms). Both TAK-390 and T-168391 decreased CYP2C19 isoform-specific activity with IC₅₀ values of 10 µmol/L and 1 µmol/L, respectively. Both TAK-390 and T-168391 did not have any effects on other CYP isoform-specific metabolic activities (including CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9(Arg), 2C9(Cys), 2D6, 2E1, and 3A4) at up to 10 µmol/L.

2.6.4.6 Excretion

More than 95% of the radioactivity given was recovered from the excreta as metabolites within 72 hours in both rats and dogs after oral administration of ¹⁴C-TAK-390. Approximately 13-15% of the administered radioactivity was excreted in urine and 81-83% in feces. Approximately 65% of an intraduodenal dose was secreted into the bile of biliary-cannulated rats within 24 hours, suggesting that the radioactivity is predominantly excreted into feces via the biliary route.

2.6.6 TOXICOLOGY

2.6.6.3 Repeat-dose toxicity

Study title: Four-week oral gavage toxicity study of TAK-390 in rats

Study no.: 00-367/SU

Conducting laboratory and location:

Drug Safety Laboratories
Pharmaceutical Research Division
Takeda Chemical Industries, Ltd.
Osaka, Japan

Date of study initiation: November 20, 2000

GLP compliance: This study was conducted by Takeda Chemical Industries, Ltd in Japan in accordance with the Good Laboratory Practice (GLP) Regulation promulgated by the Ministry of Health and Welfare of Japan.

QA report: yes (x) no ()

Drug, lot #, and % purity: M390-002, 99.7%

Methods

Doses: TAK-390: 0, 15, 50, and 150 mg/kg/day for 4 weeks.

AG-1749 (racemic lansoprazole): 150 mg/kg/day for 4 weeks.

T-168391 (S(-) isomer): 15, 50, and 150 mg/kg/day for 4 weeks.

Species/strain: (b) :Wistar rats

Age: 5 weeks

Weight: 102-121 g for males and 85-102 g for females.

Number/sex/group or time point (main study): 10

Route, formulation, volume, and infusion rate: Oral gavage, 5 ml/kg, 5% (w/v) of gum Arabic solution was used for vehicle for the control group and treatment groups. The pH of the solution was adjusted to 6.9-7.1 with 0.1 N KOH.

Satellite groups used for toxicokinetics:

4 animals/sex/group were used for the following toxicokinetic groups:

TAK-390: 15, 50, and 150 mg/kg/day.

AG-1749 (racemic lansoprazole): 150 mg/kg/day.

T-168391 (S(-) isomer): 15, 50, and 150 mg/kg/day. Plasma levels of test drugs were determined on days 1 and 29 at 0.25, 0.5, 1, 2, 6, and 24 hours after dosing.

There were no recovery groups.

Observations and times:

- **Clinical signs:** Clinical signs of toxicity were observed daily.
- **Body weights:** Body weights were determined before treatment, on day 1, and twice a week during weeks 1-4.
- **Food consumption:** Food consumption was determined weekly.
- **Ophthalmoscopy:** Before dosing and during week 4.
- **Clinical chemistry and hematology:** Clinical chemistry and hematology were conducted at termination.
- **Urinalysis:** During week 4.
- **Toxicokinetics:** Plasma levels of test drugs were determined on days 1 and 29 at 0.25, 0.5, 1, 2, 6, and 24 hours after dosing.
- **Gross pathology:** Animals were necropsied at termination.
- **Organ weight:** Adrenal, brain, ovaries, spleen, heart, testes, kidney, liver, thymus, pituitary, stomach, ventral prostate, and lungs were weighed.

- **Histopathology:** Histopathological examination was conducted in the following tissues in all animals:

- | | |
|--------------------------|----------------------------------|
| - brain | - pituitary gland |
| - spinal cord | - heart |
| - aorta | - lungs |
| - liver | - pancreas |
| - spleen | - kidneys |
| - adrenal glands | - sublingual glands |
| - submandibular glands | - submandibular lymph nodes |
| - thymus | - thyroid |
| - parathyroids | - tongue |
| - trachea | - esophagus |
| - stomach | - duodenum |
| - jejunum | - ileum |
| - cecum | - colon |
| - mesenteric lymph nodes | - urinary bladder |
| - testes | - epididymides |
| - prostate | - seminal vesicles |
| - ovaries | - oviducts* |
| - uterus | - vagina |
| - eyes | - extra orbital lacrimal glands* |
| - Harderian glands | - Zymbal's glands* |
| - nose* | - skin |
| - mammary glands | - femur |
| - sternum | - bone marrow |
| - skeletal muscle | - sciatic nerve |

To assess the repeated dose toxicity of TAK-390 in rats, TAK-390 was given to rats by oral gavage at 0, 15, 50, and 150 mg/kg/day for 4 weeks. T-168391 (S(-) isomer) was also given by oral gavage to rats at 15, 50, and 150 mg/kg/day. Another group of rats received recemic lansoprazole, AG-1749, at 150 mg/kg/day by oral gavage. Clinical signs of toxicity were observed daily. Body weights were determined before treatment, on day 1, and twice a week during weeks 1-4. Food consumption were determined weekly. Hematology, clinical chemistry, and urinalysis were conducted at termination. Plasma levels of test drugs were determined on days 1 and 29 at 0.25, 0.5, 1, 2, 6, and 24 hours after dosing. Ophthalmological examination was conducted before treatment and during week 4. All animals were necropsied at termination and organ weights were determined. Histopathological examination was conducted in all animals in all groups.

Results:

Mortality: One female from 150 mg/kg/day group for TAK-390 was found dead on day 10. This animal had 10 calculi in the urinary bladder, urine retention, and distension in the urinary bladder, dilation of the pelvis in the right kidney, large adrenal gland, and small thymus. The calculi in the urinary bladder were considered as the cause of death. However, since calculi were noted in the kidney or urinary bladder in the control animals, this change was not considered treatment related.

Clinical signs: There were no treatment related changes.

Body weights: The mean initial and final body weights in control animals were 111 and 302 g for males or 94 and 185 g for females, respectively. Treatment with TAK-390 reduced terminal body weight gain by 14% in females or 20% in males at high dose of 150 mg/kg/day. The terminal body weight gain was decreased by 11% in females or 19% in males in group of racemic lansoprazole. The terminal body weight gain was also decreased by 18% in females or 15% in males in group of T-168391 (S(-) isomer).

Food consumption: The mean food consumption in the control animals was 18-24 g/animal/day for males or 14.4-16.3 g/animal/day for females. Slight decreased food consumption was found in the high dose groups (16.8-21 g/animal/day for males and 14-15.6 g/animal/day for females) as compared to the control.

Ophthalmoscopy: There were no treatment related changes.

Hematology: Decrease in hematocrit (2.8-4%), mean corpuscular volume (5.7-5.8%), and platelet counts (9%) were noted in the high dose group (TAK-390, 150 mg/kg/day). Similar changes were also found in the 150 mg/kg/day groups of T168391 and AG-1749.

Clinical chemistry: Slight increase in total cholesterol (~9-25%) and urea nitrogen (11-25%) were noted in the high dose groups of TAK-390, T168391, and AG-1749. Creatinine and bilirubin were not affected.

Urinalysis: There were no treatment related changes.

Gross pathology: Small thymus was noted in one female in the 150 mg/kg/day group of TAK-390.

Organ weights: The thymus and pituitary weight to body weight ratios were decreased by ~37-45% (thymus) and 8-14% (pituitary) in the high dose groups of TAK-390, AG-1749, and T168391 (150 mg/kg/day). The liver and stomach weight to body weight ratios were increased by ~18-21% (liver) and 13-31% (stomach) in the high dose groups of TAK-390, AG-1749, and T168391 (150 mg/kg/day).

Histopathology: Histopathological examination revealed eosinophilic change in chief cells and vacuolization in parietal cells of the stomach in all treatment groups including TAK-390, T-168391, and racemic lansoprazole with higher incidences at high dose groups of 150 mg/kg/day. The severity and incidence of these histopathological changes were comparable in the groups of TAK-390, T-168391, and racemic lansoprazole. The results of these changes are summarized in the following table.

Incidence of histopathological changes in the stomach

	Eosinophilic changes in chief cells		Vacuolization of parietal cells	
	Male	Female	Male	Female
control	0	minimal	0	0
TAK-390 15 mg/kg	6	minimal	3	0
TAK-390 50 mg/kg	9	minimal	6	0
TAK-390 150 mg/kg	3	minimal	6	0
	7	mild	1	0
AG-1749 150 mg/kg	1	minimal	4	4
	9	mild	4	0
T168391 15 mg/kg	1	minimal	4	0
T168391 50 mg/kg	3	minimal	3	0
T168391 150 mg/kg	7	minimal	7	2
	1	mild	0	0

Hypertrophy of centrilobular hepatocytes was noticed in the high dose groups of TAK-390, T-168391, and the group of racemic lansoprazole.

Toxicokinetics: Following oral dose of TAK-390, no T-168391 was detected in the plasma. The plasma level of TAK-390 was accumulated over time following doses of 15 and 50 mg/kg/day. TAK-390 was the major compound detected in the plasma after oral dose of lansoprazole. The results were summarized in the following table.

Toxicokinetic parameters of TAK-390 and T-168391

Dose		TAK-390			T-168391		
	mg/kg	Tmax, h	Cmax, ng/ml	AUC, ng.h/ml	Tmax, h	Cmax, ng/ml	AUC, ng.h/ml
TA	15, D1	0.25	406	253	-	0	0
	15, D29	0.29	405	332	-	0	0
	50, D1	0.25	1874	1489	0.29	8	3
	50, D29	0.29	3081	3226	-	0	0
	150, D1	0.25	4312	3590	-	0	0
	150, D29	0.54	6548	11274	-	0	0
L	150, D1	0.5	2319	7743	0.38	275	744
	150, D29	2	1236	7819	2.33	146	733
T	15, D1	0.79	39	42	0.25	19	5
	15, D29	0.5	52	50	0.13	111	37
	50, D1	0.46	121	159	0.29	457	289
	50, D29	0.25	70	65	0.13	389	180
	150, D1	0.54	272	440	0.38	1094	620
	150, D29	0.42	72	57	0.29	1075	1000

TA = TAK-390, L = racemic Lansoprazole, T = T-168391,

D1 = Day 1, D29 = day 29, AUC = AUC_{0-24hour}

The C_{max} and AUC_∞ were 4507 ng/ml and 11425 ng.h/ml, respectively, following 90 mg oral dose of TAK-390 delayed release capsules in healthy human volunteers in study C02-004.

In summary, in the 4-week oral toxicity study in rats, Wistar rats were treated by oral gavage with TAK-390 and T-168391 (S(-) isomer) at 0, 15, 50, and 150 mg/kg/day for 4 weeks. Another group of rats received racemic lansoprazole at 150 mg/kg/day by oral gavage. There were no treatment related changes in mortality, clinical signs of toxicity, ophthalmology, and urinalysis. Treatment with TAK-390 reduced terminal body weight gain by 14% in females and 20% in males at high dose of 150 mg/kg/day. The terminal body weight gain was also decreased by 11% in females and 19% in males in group of racemic lansoprazole. Histopathological examination revealed eosinophilic change in chief cells and vacuolization in parietal cells of the stomach in all treatment groups including TAK-390, T-168391, and racemic lansoprazole with higher incidences at high dose groups of 150 mg/kg/day. Hypertrophy of centrilobular hepatocytes was noticed in the high dose groups of TAK-390, T-168391, and the group of racemic lansoprazole. The

severity and incidence of these histopathological changes were comparable in the groups of TAK-390, T-168391, and racemic lansoprazole. The stomach was the target organ of toxicity. No effect dose was not identified. TAK-390 was tolerated at doses up to 50 mg/kg/day.

Study title: Thirteen-week oral gavage toxicity study of TAK-390 in rats

Study no.: B-5278

Conducting laboratory and location:

(b) (4)

Date of study initiation: February 12, 2004

GLP compliance: This study was conducted by Takeda Chemical Industries, Ltd in Japan in accordance with the Good Laboratory Practice (GLP) Regulation promulgated by the Ministry of Health and Welfare of Japan.

QA report: yes (x) no ()

Drug, lot #, and % purity: M390-010, 98.9%

Methods

Doses: TAK-390: 0, 5, 15, and 50 mg/kg/day for 13 weeks.

AG-1749 (racemic lansoprazole): 50 mg/kg/day for 13 weeks.

Species/strain: (b) :Wistar rats

Age: 5 weeks

Weight: 118-137 g for males and 95-112 g for females.

Number/sex/group or time point (main study): 10

Route, formulation, volume, and infusion rate: Oral gavage, 5 ml/kg, 5% (w/v) of gum Arabic solution was used as the vehicle for the control and treatment groups. The pH of the solution was adjusted to 7 with 0.1 N KOH.

Satellite groups used for toxicokinetics:

4 animals/sex/group were used for the following toxicokinetic groups:

TAK-390: 5, 15, and 50 mg/kg/day.

AG-1749 (racemic lansoprazole): 50 mg/kg/day.

Plasma levels of test drugs were determined on days 1 and 87 at 0.25, 0.5, 1, 2, 6, and 24 hours after dosing.

There were no recovery groups.

Observations and times:

- Clinical sings: Clinical signs of toxicity were observed daily.

- Body weights: Body weights were determined before treatment, on day 1, and twice a week during the study.
- Food consumption: Food consumption was determined weekly.
- Ophthalmoscopy: Before dosing and at the termination.
- Clinical chemistry and hematology: Clinical chemistry and hematology were conducted at termination.
- Urinalysis: before treatment and during week 13.
- Gross pathology: Animals were necropsied at termination.
- Organ weight: Adrenal, brain, ovaries, spleen, heart, testes, kidney, liver, salivary glands, thymus, pituitary, stomach, prostate, and lungs were weighed.
- Histopathology: Histopathological examination was conducted in the following tissues in all animals:

cerebrum, cerebellum, spinal cord (thoracic), sciatic nerves#, eyeballs*, optic nerves*, Harderian glands*, pituitary, thyroids*, parathyroids*, adrenals*, thymus, spleen, submandibular lymph node, mesenteric lymph node, heart, thoracic aorta, trachea, lungs (including bronchus), tongue, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular glands*, sublingual glands*, liver, pancreas, kidneys*, urinary bladder, testes*, epididymides*, prostate, seminal vesicles#, ovaries*, uterus (both horns)*, vagina, mammary glands (inguinal region, both sides)#, sternum (including bone marrow), femurs (including bone marrow)#, femoral muscles# and skin (inguinal, both sides)#

Results:

Mortality: There were no deaths.

Clinical signs: There were no treatment related changes.

Body weights: There were no treatment related changes.

Food consumption: There were no treatment related changes.

Ophthalmoscopy: There were no treatment related changes.

Hematology: Decrease in hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, neutrophil ratio and lymphocyte ratio were noted in the high dose group (TAK-390, 50 mg/kg/day). Similar changes were also found in the 50 mg/kg/day group of AG-1749. The results were presented in the following table.

Text Table 1. Summary of hematology

Sex Test article	Male				Female			
	TAK-390			Lanso- prazole	TAK-390			Lanso- prazole
Dose (mg/kg/day)	5	15	50	50	5	15	50	50
No. of animals	10	10	10	10	10	10	10	10
Hb	N	N	-4%*	-5%	N	N	N	N
Ht	N	N	-2%*	-4%	N	N	N	N
MCV	N	N	-2%*	-2%	N	-2%*	-2%*	-3%**
MCH	N	N	-2%*	-2%*	-2%*	-3%*	-3%*	-4%**
Lymphocyte ratio	N	N	N	N	N	N	+9%*	N
Stab-form ratio	N	N	N	N	N	N	-67%*	N
Segmented ratio	-22%*	N	N	N	N	N	-36%*	N
Eosinophil ratio	N	N	N	N	N	N	-60%*	-53%*

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).

N: No remarkable changes.

* (***) $p \leq 0.05$ (0.01) (significantly different from the control group)

Clinical chemistry: Slight increase in total cholesterol and urea nitrogen were noted in the high dose groups of TAK-390 and AG-1749. The results were presented in the following table.

Text Table 2. Summary of blood chemistry

Sex Test article	Male				Female			
	TAK-390			Lanso- prazole	TAK-390			Lanso- prazole
Dose (mg/kg/day)	5	15	50	50	5	15	50	50
No. of animals	10	10	10	10	10	10	10	10
LDH	N	N	N	N	N	N	+20%	+20%*
T.cho	N	N	N	N	N	N	-9%*	-9%
BUN	N	+14%*	N	N	N	N	N	N
Na	N	N	N	N	+1%*	N	N	N
Cl	N	N	-1%*	-2%**	N	N	-1%*	-1%*
TP	N	N	N	N	+5%*	N	N	N
Albumin	N	N	N	N	+7%*	+4%*	+7%*	+4%*
A/G	N	N	N	N	N	N	+4%*	+3%*

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).

N: No remarkable changes.

* (***) $p \leq 0.05$ (0.01) (significantly different from the control group)

Urinalysis: There were no treatment related changes.

Gross pathology: There were no treatment related changes.

Organ weights: The thymus and pituitary weights were decreased in the high dose groups of TAK-390 and AG-1749. The liver and stomach weights were increased in the high dose groups of TAK-390 and AG-1749. The results were summarized in the following table.

Text Table 3. Summary of organ weights

Sex Test article	Male				Female			
	TAK-390			Lanso- prazole	TAK-390			Lanso- prazole
Dose (mg/kg/day)	5	15	50	50	5	15	50	50
No. of animals	10	10	10	10	10	10	10	10
Body weight at necropsy	N	N	N	N	N	N	N	N
Pituitary								
Absolute	N	N	N	N	N	N	-6%	-11%**
Relative	N	N	N	N	N	N	-10%*	-13%**
Salivary gland								
Absolute	N	N	N	N	N	N	N	N
Relative	N	N	N	N	N	N	N	-8%*
Thymus								
Absolute	N	-13%*	-35%*	-32%**	N	N	-21%*	-19%**
Relative	N	N	-32%*	-30%**	N	N	-22%*	-21%**
Heart								
Absolute	N	N	N	N	N	N	N	N
Relative	N	N	N	-7%*	N	N	N	N
Lung								
Absolute	N	N	+5%*	+8%*	N	N	N	N
Relative	N	+3%*	+7%*	+7%*	N	N	N	N
Liver								
Absolute	N	N	+7%	+8%*	N	N	+14%*	+11%**
Relative	N	N	+9%*	+9%**	N	N	+12%*	+7%**
Stomach								
Absolute	+18%*	+23%*	+20%*	+22%**	+23%*	+23%*	+24%*	+24%**
Relative	+20%*	+24%*	+22%*	+24%**	+17%*	+23%*	+21%*	+21%**
Ovary								
Absolute	NA	NA	NA	NA	N	N	N	+19%*
Relative	NA	NA	NA	NA	N	N	N	+15%*

Values in the table indicate percentage of change against the control mean (+: increase, -: decrease).

N: No remarkable changes.

NA: No applicable.

* (***) p≤0.05 (0.01) (significantly different from the control group)

Histopathology: Histopathological changes were in the liver and stomach. The results of these changes are summarized in the following table.

Text Table 4. Incidence summary of histopathology

Sex Test article	Male					Female					
	TAK-390				Lanso- prazole	TAK-390				Lanso- prazole	
Dose (mg/kg/day)		0	5	15	50	50	0	5	15	50	50
No. of animals		10	10	10	10	10	10	10	10	10	10
Liver											
Hypertrophy, hepatocyte, central	(±)	0	0	0	6	2	0	0	0	2	3
Stomach											
Eosinophilia, chief cell	(±)	0	4	9	5	5	0	0	4	9	4
	(+)	0	0	0	5	4	0	0	0	1	0

Values in the table indicate the incidence.

±: Slight, +: Mild

Toxicokinetics: It appears that the test drugs were accumulated over time. The results were summarized in the following table.

Thirteen-week oral gavage toxicity study of TAK-390 in rats (B-5278)(2/2)

Animal	(b) Wistar rats, 5 weeks of age				
Test article	Control ^{a)}	TAK-390			Lansoprazole
Dosage level (mg/kg/day)	0	5	15	50	50
Dosage volume (mL/kg/day)	5	5	5	5	5
No. of animals (M:F) ^{b)}	10:10	10:10	10:10	10:10	10:10
Mortality (M:F)	0:0	0:0	0:0	0:0	0:0
Plasma drug concentrations (n=3)					
TAK-390					
T _{max} (h)	Day 1 (M/F)	0.3/0.3	0.3/0.3	0.3/0.3	0.3/0.8
	Week 13 (M/F)	0.3/0.3	0.3/0.3	0.3/0.3	1.2/1.0
C _{max} (ng/mL)	Day 1 (M/F)	84/158	203/627	1123/2660	677/1186
	Week 13 (M/F)	307/638	1139/1502	2770/6619	438/1338
AUC _{0-24h} (ng·h/mL)	Day 1 (M/F)	46/81	130/622	876/2809	907/2281
	Week 13 (M/F)	197/546	876/1974	2210/9337	1808/5030
T-168391					
T _{max} (h)	Day 1 (M/F)	NC/NC	NC/NC	NC/NC	0.3/0.3
	Week 13 (M/F)	NC/NC	NC/NC	NC/NC	1.2/0.8
C _{max} (ng/mL)	Day 1 (M/F)	0/0	0/0	0/0	51/102
	Week 13 (M/F)	0/0	0/0	0/0	24/113
AUC _{0-24h} (ng·h/mL)	Day 1 (M/F)	0/0	0/0	0/0	57/142
	Week 13 (M/F)	0/0	0/0	0/0	75/369
Conclusion	Non-toxic dosage level: 15 mg/kg/day for males and females Comparison of toxicity between TAK-390 and Lansoprazole: almost the same				

a): 5 w/v% Gum arabic solution whose pH was adjusted to approximately 7 by adding 0.1 mol/L KOH solution

M: Male, F: Female

b): Additional 4 animals/sex/dose were used as satellite groups for toxicokinetics except for the control group.

NC: Not calculated (plasma concentration was below the quantification limit)

In summary, in the 13-week oral toxicity study in rats, Wistar rats were treated by oral gavage with TAK-390 at 0, 5, 15, and 50 mg/kg/day for 13 weeks. Another group of rats received racemic lansoprazole at 50 mg/kg/day for 13 weeks. There were no treatment related changes in mortality, clinical signs of toxicity, body weight, ophthalmology, and urinalysis. Histopathological examination revealed eosinophilic change in chief cells of the stomach and liver hypertrophy in all treatment groups including TAK-390 and racemic lansoprazole. The stomach was the target organ of toxicity. No effect dose was not identified. TAK-390 was tolerated at doses up to 50 mg/kg/day.

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Study title: Thirteen-week oral gavage toxicity study of TAK-390 in dogs

Study no.: B-5277

Conducting laboratory and location:

(b) (4)

Date of study initiation: January 16, 2004

GLP compliance: This study was conducted by Takeda Chemical Industries, Ltd in Japan in accordance with the Good Laboratory Practice (GLP) Regulation promulgated by the Ministry of Health and Welfare of Japan.

QA report: yes (x) no ()

Drug, lot #, and % purity: M390-010, 98.9%

Methods

Doses: TAK-390: 0, 5, 15, and 50 mg/kg/day for 13 weeks.

AG-1749 (racemic lansoprazole): 50 mg/kg/day for 13 weeks.

Species/strain: beagle dogs

Age: 5-6 months

Weight: 8.5-10.6 kg for males and 8.1-9.7 kg for females.

Number/sex/group or time point (main study): 3

Route, formulation, volume, and infusion rate: Oral capsule

Plasma levels of test drugs were determined on days 1, 28, and 91 at 0.5, 1, 2, 4, 8, and 24 hours after dosing.

Observations and times:

- Clinical signs: Clinical signs of toxicity were observed daily.
- Body weights: Body weights were determined before treatment, on day 1, and twice a week during the study.
- Food consumption: Food consumption was determined weekly.
- Ophthalmoscopy: Before dosing and at the termination.
- Clinical chemistry and hematology: Clinical chemistry and hematology were conducted at termination.
- Urinalysis: before treatment and during week 13.
- Body temperature: Rectal temperature was determined.
- ECG: before treatment and during weeks 4, 7, and 13.
The ECG was monitored before dosing, 1-2 hours and 5-6 hours after dosing.
- Gross pathology: Animals were necropsied at termination.
- Organ weight: Adrenal, brain, ovaries, spleen, heart, testes, kidney, liver, salivary glands, thymus, pituitary, stomach, prostate, and lungs were weighed.

- Histopathology: Histopathological examination was conducted in the following tissues in all animals:

Text-Table 8. Pathological Examination

Organ/tissue	Examination	Weighing
	HE	
Cerebrum	0	} 0
Cerebellum	0	
Medulla oblongata	0	
Spinal cord	0	
Optic nerve	0	
Sciatic nerve	0	
Eyeball	0	
Lacrimal gland	0	
Pituitary	0	0
Thyroid gland	0	0
Parathyroid	0	
Adrenal gland	0	0
Thymus	0	0
Spleen	0	0
Submandibular lymph node	0	
Mesenteric lymph node	0	
Heart	0	0
Aorta (aortic arch)	0	
Larynx	0	
Trachea	0	
Lung (including bronchial tubes)	0	0
Tongue	0	
Esophagus	0	
Stomach	0	0
Duodenum	0	

Organ/tissue	Examination	Weighing
	HE	
Jejunum	0	
Ileum	0	
Cecum	0	
Colon	0	
Rectum	0	
Submandibular gland	0	0
Sublingual gland	0	
Parotid gland	0	
Liver	0	} 0
Gallbladder	0	
Pancreas	0	0
Kidney	0	0
Urinary bladder	0	
Testis/ovary (oviduct)	0	0/0(-)
Epididymis/uterus	0	0/0
Prostate/vagina	0	0/
Mammary gland	0	
Sternum (including bone marrow)	0	
Femur (including bone marrow)	0	
Femoral skeletal muscle	0	
Skin (abdominal)	0	
Diaphragm	0	
Additional gross lesions ^{a)}	0	
Parts for identification (auricle)	(preservation only)	

H/E: Hematoxyline/Eosin Stain

a): 3003: oral mucosa, internal iliac and mediastinal lymph nodes; 5002: knee joint of both sides, oral mucosa and cervical and thoracic cords; 3101: diaphragm and greater omentum

Results:

Mortality: There were no deaths.

Clinical signs: Soft/mucous feces (5 mg/kg/day or higher) or watery feces (50 mg/kg/day) were noted during the study. Vomiting was noted in all treatment groups particularly after the first dose. Similar changes were also noted in the lansoprazole group.

Body weights: The initial and final body weights of the control animals were 9.6 kg and 11.5 kg in males and 8.7 kg and 10.5 kg in females, respectively. There were no treatment related changes.

Food consumption: There were no treatment related changes.

Ophthalmoscopy: There were no treatment related changes.

Hematology: There were no treatment related changes.

Clinical chemistry: There were no treatment related changes.

Urinalysis: There were no treatment related changes.

Body Temperature: There were no treatment related changes.

ECG: There were no treatment related changes.

Liver Enzymes: Treatment with TAK-390 and lansoprazole activated the hepatic enzymes ethoxyresorufin *O*-deethylation and aminopyrine *N*-demethylation (see table below).

2.6.7.7.C Repeat-Dose Toxicity Study No. B-5277 (Cont.) Test Article: Dexlansoprazole

Test Article	Vehicle				TAK-390				Lansoprazole ^a	
	0		5		15		50		50	
Daily Dose (mg/kg/day)	M	F	M	F	M	F	M	F	M	F
Number of Animals	3	3	3	3	3	3	3	3	3	3
Noteworthy Findings (Cont.)										
Histopathology Incidence ^b										
No. Examined	3	3	3	3	3	3	3	3	2	3
Stomach										
Vacuolation of parietal cells - Slight	0	0	1	0	1	2	2	0	1	3
Vacuolation of parietal cells - Mild	0	0	0	0	0	0	1	2	0	0
Necrosis of parietal cells - Slight	0	0	0	0	1	0	1	3	2	2
Liver										
Bile thrombus in bile canaliculus - Slight	0	0	0	0	0	1	1	0	1	1
Additional Examinations										
Hepatic Drug-Metabolizing Enzymes ^c (Terminal dogs only)										
APD (nmol/g liver/min)	--	67	--	85	--	89*	--	108*	--	94
APD (nmol/mg protein/min)	--	0.47	--	0.66*	--	0.73*	--	0.81*	--	0.77 [†]
EROD (nmol/g liver/min)	1.12	1.06	10.18*	8.09*	11.01*	13.30*	11.17*	14.73*	18.94	11.84 [‡]
EROD (nmol/mg protein/min)	0.0083	0.0075	0.0844*	0.0638*	0.0868*	0.1087*	0.0903*	0.1103*	0.1478	0.0977 [‡]

-- No treatment-related effects

Statistical Significance: *p≤0.05 (Shirley-Williams' test); [†]p≤0.05 (Student's t-test); *p≤0.05 (Williams' test); [‡]p≤0.05 (Aspin-Welch t-test)

a Lansoprazole is a racemate consisting of TAK-390 [R(+) isomer] and T-168391 [S(-) isomer].

b Moribund sacrifice of lansoprazole male on day 29 due to subdural hemorrhage in the brain believed to be caused by spontaneous polyarteritis (1+ severity). One other dog (male, 15 mg/kg/day TAK-390) exhibited polyarteritis and meningitis with/without hemorrhage in cervical cord and dura matter of the brain upon microscopic examination. Lesions not test article-related.

i n=2 for lansoprazole males n=3 all others.

Abbreviations: APD - aminopyrine *N*-demethylation; EROD - ethoxyresorufin *O*-deethylation; F - Female; M - Male

Gross pathology: Thicken gastric wall was noted in the treatment groups (see table below).

2.6.7.7.C Repeat-Dose Toxicity		Study No. B-5277 (Cont.)				Test Article: Dexlansoprazole				
Test Article	Vehicle		TAK-390				Lansoprazole ^a			
Daily Dose (mg/kg/day)	0		5		15		50		50	
	M	F	M	F	M	F	M	F	M	F
Number of Animals ^b	3	3	3	3	3	3	3	3	3	3
Noteworthy Findings (Cont.)										
Ophthalmology										
No treatment-related effects	--	--	--	--	--	--	--	--	--	--
Electrocardiogram										
No treatment-related effects	--	--	--	--	--	--	--	--	--	--
Hematology										
No treatment-related effects	--	--	--	--	--	--	--	--	--	--
Blood Chemistry										
No treatment related effects	--	--	--	--	--	--	--	--	--	--
Urinalysis										
No treatment-related effects	--	--	--	--	--	--	--	--	--	--
Organ Weights^c										
Liver	294.5 g	234.3 g	+10.2	+13.7	-0.4	+18.5	+15.5*	+27.2	+14.2	+17.6
Stomach	116.31 g	89.75 g	+25.0	+18.1	+31.7	+42.7*	+65.9*	+50.4*	+53.6	+52.3 ^g
Gross Necropsy (Incidence)										
Stomach										
Thickened wall	0	0	0	0	1	1	2	1	1	2
-- No treatment-related effects										

Statistical Significance: * $p \leq 0.05$ (Williams' test); [†] $p \leq 0.05$ (Student's t-test).

a Lansoprazole is a racemate consisting of TAK-390 [R(+) isomer] and T-168391 [S(-) isomer].

g Both absolute and relative organ weights differ from controls in the direction indicated. For controls, group means are shown and for treated groups percent difference from controls are shown. Statistical difference based on actual weights and not percent difference.

Abbreviations: F - Female; M - Male.

Organ weights: The liver and stomach weights were increased in the treatment groups (see table above).

Histopathology: Histopathological changes were in the liver (bile thrombus, 1 male each at high dose of both TAK-390 and lansoprazole and 1 female each at mid dose TAK-390 and lansoprazole) and stomach (vacuolation and necrosis of parietal cells) in all treatment groups including lansoprazole. The incidence of histopathological changes in the stomach is summarized in the following table.

Incidence of histopathological changes in the stomach

	Vacuolization of parietal cells		Necrosis of parietal cells	
	Male	Female	Male	Female
control	0	0	0	0
TAK-390 5 mg/kg	1	0	0	0
TAK-390 15 mg/kg	1	2	1	0
TAK-390 50 mg/kg	3	2	1	3
AG-1749 50 mg/kg	1	3	2	2

The severity of the histopathological changes in the stomach was dose dependent.

Toxicokinetics: It appears that the plasma level of test drug was decreased over time. The results were summarized in the following table.

Animal		Beagle dogs, 6 months old				
Test article	Cont. ^{a)}	TAK-390			Lansoprazole	
Dose (mg/kg/day)	0	5	15	50	50	
No. of animals (M:F)	3:3	3:3	3:3	3:3	3:3	
(b) (4) (M:F)	-	(0:2)	Aminopyrine <i>N</i> -demethylation ↑ (1:3) (2:3)		(1:3)	
		(3:3)	Ethoxyresorufin <i>O</i> -deethylation ↑ (3:3) (3:3)		(2:3)	
TK (TAK-390; M:F)						
T _{max} (h)	1st	2.0:1.7	2.3:1.7	2.0:2.3	1.7:1.3	
	28th	0.8:0.7	1.3:0.7	1.7:0.7	2.0:1.3	
	91st	0.8:0.7	0.7:1.7	2.0:1.7	2.0:1.3	
C _{max} (ng/mL)	1st	289:444	1580:756	1508:1430	961:1769	
	28th	53:679	100:369	1037:1618	148:125	
	91st	14:80	734:216	609:1159	194:497	
AUC _{0-24h} (ng·h/mL)	1st	513:895	3518:1303	3436:3639	2323:3921	
	28th	69:1355	247:633	2888:3328	412:452	
	91st	16:87	1263:542	1703:2725	499:1347	
TK (T-168391; M:F)						
T _{max} (h)	1st	2.0:1.0	2.3:1.7	1.7:2.0	1.7:1.0	
	28th	-:1.0	1.0:-	2.0:1.0	2.0:1.3	
	91st	1.0:0.8	0.8:1.3	1.3:1.0	2.0:1.7	
C _{max} (ng/mL)	1st	11:20	72:58	55:70	174:366	
	28th	0:0	2:0	0:2	48:36	
	91st	1:2	5:16	6:3	68:198	
AUC _{0-24h} (ng·h/mL)	1st	19:33	139:88	133:138	436:709	
	28th	0:0	2:0	1:2	140:132	
	91st	1:2	4:29	8:4	168:525	
Conclusion	Non-toxic dose level of TAK-390: 5 mg/kg/day Toxic potential of TAK-390 at 50 mg/kg is equivalent to or lower than Lansoprazole at 50 mg/kg.					

a): empty gelatin capsule, M: male, F: female, **(b) (4)**

Assay, ↑: increase, -: the values were less than the quantification limit, Number in parenthesis indicates the number of animals that showed the change

In summary, in the 13-week oral toxicity study in dogs, Beagle dogs were treated by oral capsule with TAK-390 at 0, 5, 15, and 50 mg/kg/day for 13 weeks. Another group of dogs received racemic lansoprazole at 50 mg/kg/day for 13 weeks. There were no treatment related changes in mortality, body weight, ophthalmology, ECG, hematology, clinical chemistry, and urinalysis. Clinical signs of toxicity such as vomiting and soft/watery feces were noted in the treatment groups. Blood pressure was not monitored. Histopathological examination revealed vacuolation and necrosis of parietal cells of stomach in all treatment groups including lansoprazole. In the liver, bile thrombus was also noted in one male each at high dose of both TAK-390 and lansoprazole and one female each at mid dose TAK-390 and lansoprazole. The liver and stomach were the target

organs of toxicity. No effect dose was not identified. TAK-390 was tolerated at doses up to 50 mg/kg/day.

2.6.6.4 Genetic toxicology

Study title: Ames test with TAK-390

Study report No: study code: K01-3615

Testing Laboratory: (b) (4)

Date of study initiation: September 13, 2006

Date of study report: December 5, 2006

GLP Compliance: This study was conducted in accordance with "standard to be observed by testing institutions for toxicity investigations" by Ministry of Labor of Japan, Notification No 76.

QA-report: Yes (x) No ()

Drug Batch No.: M390-028

Study Endpoint: To determine the potential mutagenic effects of TAK-390.

Methods: To examine the potential mutagenic effects of TAK-390, the reverse mutation assay (Ames test) was conducted using pre-incubation method in four strains *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and one strain of *E. Coli* (WP2uvrA) in the presence and absence of metabolic activator, S-9 mix from rat liver. The following concentrations were tested: 39.1, 78.1, 156, 313, 625, 1250, 2500, and 5000 µg/plate with and without S-9. Following positive controls were tested:

	TA100	TA1535	WP2uvrA	TA98	TA1537
-S9 mix	AF-2	NaN ₃	AF-2	AF-2	ICR-191
	0.01	0.5	0.01	0.1	0.5
+S9 mix	2AA	2AA	2AA	2AA	2AA
	1	2	10	0.5	2

(Unit: µg/plate)

2AA = 2-Aminoanthracene

AF-2 = 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide

NaN₃ = Sodium azide

ICR-191 = 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine·2HCl

- **Negative control:** Dimethyl sulfoxide.

- **Counting method:** The plates were observed macroscopically using a stereomicroscope.

- **Cytotoxic endpoints:** The condition of the bacterial background lawn was evaluated for evidence of cytotoxicity.

- **Genetic toxicity endpoints/results:** Number of revertant colonies.

- **Statistical methods:** Revertant colonies were averaged for each concentration.

Criteria for positive results: The results should be considered positive if the test substance induced a two fold increase in the mean revertant colonies as compared to the control and this increase should be a dose response to increasing concentrations of the test article.

Results:

- Study validation: The positive controls significantly increased the revertant colonies compared to the solvent controls.

- Study outcome: Treatment with test article significantly increased the revertant colonies (more than 2 folds) in TA1535, TA98, and WP2uvrA in the absence of S9 and in TA 1535 in the presence of S9 as compared to the controls. The results were presented in Tables 2 and 3. These tables are attached below.

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Table 2 Results of the main test

Test substance: TAK-390

Test Period		From September 21, 2006 to September 25, 2006									
With(+)-or without(-) S9 mix	Test substance dose (µg/plate)	Number of revertant colonies per plate									
		Base-pair substitution type						Frameshift type			
		TA100		TA1535		WP2uvrA		TA98		TA1537	
-S9 mix	Negative control	122	114	7	8	21	18	23	20	6	9
		104	(113)	10	(8)	18	(19)	15	(19)	12	(9)
	39.1	114		7		—		16		12	
		99	(107)	10	(9)	—		21	(19)	15	(14)
	78.1	112		12		—		21		7	
		110	(111)	13	(13)	—		25	(23)	15	(11)
	156	115		16		27		18		14	
		110	(113)	10	(13)	29	(28)	20	(19)	15	(15)
	313	145		19		37		21		16	
		138	(142)	36	(28)	31	(34)	28	(25)	12	(14)
625	151		37		43		51		13		
	147	(149)	47	(42)	37	(40)	41	(46)	10	(12)	
1250	45*		8*		43		58*		0*		
	37*	(41)	6*	(7)	29	(36)	56*	(57)	0*	(0)	
2500	—		—		37*		54*		—		
					35*	(36)	52*	(53)			
5000 †	—		—		21*		23*		—		
					23*	(22)	31*	(27)			
+S9 mix	Negative control	114	117	12	10	29	28	31	38	25	22
		109	(113)	7	(10)	37	(31)	26	(32)	29	(25)
	156	108		14		33		34		31	
		124	(116)	8	(11)	28	(31)	21	(28)	31	(31)
	313	152		6		37		19		15	
		110	(131)	6	(6)	35	(36)	28	(24)	21	(18)
	625	120		18		37		36		15	
		120	(120)	19	(19)	29	(33)	28	(32)	8	(12)
1250	94		23		38		26		7		
	118	(106)	18	(21)	37	(38)	44	(35)	6	(7)	
2500	28*		15*		26*		37*		6*		
	21*	(25)	15*	(15)	24*	(25)	33*	(35)	3*	(5)	
5000 †	3*		15*		22*		27*		1*		
	0*	(2)	8*	(12)	30*	(26)	34*	(31)	1*	(1)	
Positive control -S9 mix	Chemical	AF-2		NaN ₃		AF-2		AF-2		ICR-191	
	Dose(µg/plate)	0.01		0.5		0.01		0.1		0.5	
	Number of revertant colonies/plate	612		537		340		478		2012	
Positive control +S9 mix	Chemical	2AA		2AA		2AA		2AA		2AA	
	Dose(µg/plate)	1		2		10		0.5		2	
	Number of revertant colonies/plate	1247		265		368		419		320	
	1234	(1241)	280	(273)	349	(359)	455	(437)	314	(317)	

[Notes]

- (): The mean of each plate.
- †: Precipitate of test substance, and coloration to the plates (brown) was observed.
- *: Bacterial growth inhibition was observed.
- AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- NaN₃: Sodium azide
- ICR-191: 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine·2HCl
- 2AA: 2-Aminoanthracene

Table 3 Results of the confirmation test

Test substance: TAK-390

Test Period	From September 27, 2006 to September 29, 2006					
With(+)or without(-) S9 mix	Test substance dose (µg/plate)	Number of revertant colonies plate				
		Base-pair substitution type			Frameshift type	
		TA100	TA1535	WP2uvrA	TA98	TA1537
-S9 mix	Negative control	—	11 9 8 (9)	21 18 21 (20)	—	—
	39.1	—	11 10 (11)	—	—	—
	78.1	—	10 14 (12)	—	—	—
	156	—	4 12 (8)	21 21 (21)	—	—
	313	—	22 25 (24)	21 23 (22)	—	—
	625	—	41 35 (38)	21 28 (25)	—	—
	1250	—	6* 6* (6)	28 31 (30)	—	—
	2500	—	—	30* 34* (32)	—	—
	5000 †	—	—	22* 25* (24)	—	—
	Positive control -S9 mix	Chemical	—	NaN ₃	AF-2	—
Dose(µg/plate)		—	0.5	0.01	—	—
Number of revertant colonies/plate		—	451 483 (467)	464 447 (456)	—	—

[Notes]

- (): The mean of each plate.
- †: Precipitate of test substance, and coloration to the plates (brown) was observed.
- *: Bacterial growth inhibition was observed.
- AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- NaN₃: Sodium azide

The results were also confirmed in a separate study (study #36-278).

In conclusion, TAK-390 was genotoxic under the current testing conditions.

Study title: Chromosomal aberration test in Chinese Hamster Lung (CHL) Cells with TAK-390

Study report No: K06-1210

GLP Compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).

QA-report: Yes (x) No ()

Drug Batch No.: M390-028

Methods: To examine the potential induction of chromosomal aberrations, the in vitro chromosomal aberration test was conducted in CHL cells in the presence and absence of metabolic activation, S-9 mix from rat liver. TAK-390 was tested at 100, 120 and 140 µg/mL for the -S9 mix assay, 60.0, 80.0 and 100 µg/mL for the +S9 mix assay and 40.0, 60.0 and 80.0 µg/mL for the 24-hour assay.

The cells were exposed to the test drug for 6 hours or 24 hours. Positive controls (mitomycin C and cyclophosphamide monohydrate) were also tested. In all groups, cells were arrested in metaphase using colcemid ~2-3 hours before harvest.

- Exposure conditions: The cultures were incubated with test drug at 37° C.

- Genetic toxicity endpoints/results: cells with aberration.

- Statistical methods: Number of cells with aberration was averaged for each concentration.

Criteria for positive results: The results should be considered positive if the test substance induced a significant increase in the number of cells with chromosomal aberrations at one or more concentrations as compared to the control and this increase should be a dose response to increasing concentrations of the test article.

Results: Treatment with TAK-390 increased incidence of cells with chromosomal structural aberrations in the presence and absence of metabolic activation (S9) and this increase was dose-related.

The results were summarized in the following tables.

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Table 4 Results of chromosomal aberration test of TAK-390

Substance	Dose (µg/mL)	Treatment- recovery time (hour)	S9 mix	Relative number of cells (%)	Relative Mitotic Index ^{a)} (%)	Precipitation of test substance in medium ^{b)}			Frequency of cells with aberrations (%) ^{c)}	
						Treatment start	Treatment end	Culture end	Structural aberration	Numerical aberration
DMSO	0	6-18	-	100	100	-	-	-	1.0	1.0
TAK-390	60.0	6-18	-	88.2	139.3	-	-	-	n.o.	n.o.
	80.0	6-18	-	73.3	151.4	-	-	-	n.o.	n.o.
	100	6-18	-	62.7	188.8	-	-	-	2.0	1.0
	120	6-18	-	58.3	151.4	-	-	-	2.5	2.0
	140	6-18	-	49.3	103.8	-	-	-	6.5	1.0
	160	6-18	-	46.2	70.1	-	-	-	n.o.	n.o.
	180	6-18	-	34.2	35.5	-	-	-	n.o.	n.o.
	200	6-18	-	21.9	16.9	-	-	-	n.o.	n.o.
MMC	0.1	6-18	-	ND	ND	-	-	-	67.5	0.0
DMSO	0	6-18	+	100	100	-	-	-	1.5	0.5
TAK-390	40.0	6-18	+	94.3	102.6	-	-	-	n.o.	n.o.
	60.0	6-18	+	78.4	103.3	-	-	-	1.0	1.0
	80.0	6-18	+	62.8	102.6	-	-	-	7.0	1.5
	100	6-18	+	49.9	89.6	-	-	-	7.0	3.0
	120	6-18	+	37.8	57.5	-	-	-	n.o.	n.o.
	140	6-18	+	34.0	51.0	-	-	-	n.o.	n.o.
	160	6-18	+	29.7	18.3	-	-	-	n.o.	n.o.
	180	6-18	+	23.0	15.1	-	-	-	n.o.	n.o.
	200	6-18	+	14.3	9.2	-	-	-	n.o.	n.o.
CPA	6	6-18	+	ND	ND	-	-	-	24.0	0.5
DMSO	0	24-0	-	100	100	-	-	NA	2.0	1.5
TAK-390	10.0	24-0	-	100.5	98.8	-	-	NA	n.o.	n.o.
	20.0	24-0	-	98.8	101.3	-	-	NA	n.o.	n.o.
	40.0	24-0	-	77.5	116.3	-	-	NA	1.0	0.5
	60.0	24-0	-	53.6	63.8	-	-	NA	1.0	0.0
	80.0	24-0	-	36.9	68.8	-	-	NA	9.5	1.0
	100	24-0	-	29.5	52.5	-	-	NA	n.o.	n.o.
	120	24-0	-	12.3	d)	-	-	NA	n.o.	n.o.
MMC	0.05	24-0	-	ND	ND	-	-	NA	77.0	1.0

DMSO: dimethylsulfoxide, MMC: mitomycin C, CPA: cyclophosphamide monohydrate, ND: not detected,

n.o.: not observed, NA: not applicable

a) Mitotic index was calculated by observing 1000 cells per dose.

b) Precipitation of the test substance: -, absence; +, presence

c) The frequency of cells with chromosomal aberrations was calculated by observing 200 metaphases per dose.

d) It was not calculated, since most cells died.

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Table 5 Results of chromosomal aberration test in short-term treatments

Name of test substance : TAK-390

Treatment time (h)	39 aux	Dose (µg/mL)	Number of cells with structural chromosomal aberrations (frequency%)						Number of gaps (frequency%)	Relative number of cells (%)	Number of cells with numerical chromosomal aberrations (frequency%)				
			Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others			Total number of cells with aberrations	Number of cells observed	Polyploids	Others	Total number of cells with aberrations
6-18	-	Negative control (DMSO) 0	100	0	1	0	0	0	1	0	100	100	1	0	1
			200	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	200	2 (1.0)	0 (0.0)	2 (1.0)	
			100	2	1	0	0	0	3	0	63.5	100	0	0	0
6-18	-	100	100	1	0	0	0	1	1	61.8	100	2	0	2	
			200	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	1 (0.5)	62.7	200	2 (1.0)	0 (0.0)	2 (1.0)
			100	0	0	0	0	0	0	0	57.7	100	2	0	2
6-18	-	120	100	2	1	0	0	0	5	58.8	100	2	0	2	
			200	2 (1.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.5)	0 (0.0)	58.3	200	4 (2.0)	0 (0.0)	4 (2.0)
			100	1	2	0	1	0	4	0	52.5	100	0	1	1
6-18	-	140	100	6	2	0	0	0	9	46.0	100	0	1	1	
			200	7 (3.5)	5 (2.5)	0 (0.0)	1 (0.5)	0 (0.0)	13 (6.5)	0 (0.0)	49.3	200	0 (0.0)	2 (1.0)	2 (1.0)
			100	33	27	0	0	0	68	3	49.3	100	0	0	0
6-18	-	Positive control (MMC) 0.1	100	33	27	0	0	0	68	3	49.3	100	0	0	0
			200	65 (32.5)	113 (56.5)	0 (0.0)	0 (0.0)	0 (0.0)	135 (67.5)	3 (1.5)	49.3	200	0 (0.0)	0 (0.0)	0 (0.0)
			100	1	0	0	0	0	1	0	100	1	0	1	
6-18	-	Negative control (DMSO) 0	100	2	0	0	0	0	2	0	100	100	0	0	0
			200	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	79.1	200	1 (0.5)	0 (0.0)	1 (0.5)
			100	1	0	0	0	0	1	0	77.7	100	0	0	0
6-18	-	60.0	100	1	0	0	0	0	1	0	78.4	100	2	0	2
			200	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	65.8	200	2 (1.0)	0 (0.0)	2 (1.0)
			100	5	5	0	0	0	9	0	59.5	100	1	0	1
6-18	-	80.0	100	3	3	0	0	0	5	1	62.8	100	2	0	2
			200	8 (4.0)	8 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (7.0)	1 (0.5)	51.2	200	3 (1.5)	0 (0.0)	3 (1.5)
			100	5	4	1	0	0	9	0	48.5	100	2	2	4
6-18	-	100	100	4	2	0	0	0	5	0	49.9	100	1	1	2
			200	9 (4.5)	6 (3.0)	1 (0.5)	0 (0.0)	0 (0.0)	14 (7.0)	0 (0.0)	100	3 (1.5)	3 (1.5)	6 (3.0)	
			100	9	17	0	1	0	25	0	100	0	0	0	
6-18	-	Positive control (CPA) 5	100	7	17	0	0	0	23	0	100	1	0	1	
			200	16 (8.0)	34 (17.0)	0 (0.0)	1 (0.5)	0 (0.0)	48 (24.0)	0 (0.0)	200	1 (0.5)	0 (0.0)	1 (0.5)	

Comprised treatment-time and recovery-time.

The number of aberrant cells at each dish was shown at the first and the second lines. The total number of aberrant cells was shown at the third line.

Cell growth rate at each dish was shown at the first and the second lines. The average of them was shown at the third line.

Endoreduplication was shown at others in numerical chromosomal aberrations.

DMSO: dimethyl sulfoxide, MMC: mitomycin C, CPA: cyclophosphamide monohydrate.

Table 6 Results of chromosomal aberration test in continuous treatment

Name of test substance : TAK-390

Treatment time (h)	Dose (µg/mL)	Number of cells with structural chromosomal aberrations (frequency%)						Number of gaps (frequency%)	Relative number of cells (%)	Number of cells with numerical chromosomal aberrations (frequency%)					
		Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others			Total number of cells with aberrations	Number of cells observed	Polyploids	Others	Total number of cells with aberrations	
24-0	-	Negative control (DMSO) 0	100	0	1	0	0	0	1	0	100	100	2	0	2
			200	2 (1.0)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	4 (2.0)	0 (0.0)	200	3 (1.5)	0 (0.0)	3 (1.5)	
			100	1	0	0	0	0	1	0	77.6	100	1	0	1
24-0	-	40.0	100	1	0	0	0	0	1	0	77.4	100	0	0	0
			200	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	77.5	200	1 (0.5)	0 (0.0)	1 (0.5)
			100	2	0	0	0	0	2	0	54.2	100	0	0	0
24-0	-	60.0	100	0	0	0	0	0	0	0	53.0	100	0	0	0
			200	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	52.6	200	0 (0.0)	0 (0.0)	0 (0.0)
			100	7	1	0	0	0	8	2	35.7	100	2	0	2
24-0	-	80.0	100	7	4	0	0	0	11	3	38.1	100	0	0	0
			200	14 (7.0)	5 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	19 (9.5)	5 (2.5)	36.9	200	2 (1.0)	0 (0.0)	2 (1.0)
			100	39	60	0	0	0	74	2	100	1	0	1	
24-0	-	Positive control (MMC) 0.05	100	45	65	0	0	0	80	1	100	1	0	1	
			200	82 (41.0)	125 (62.5)	0 (0.0)	0 (0.0)	0 (0.0)	154 (77.0)	3 (1.5)	200	2 (1.0)	0 (0.0)	2 (1.0)	

Comprised treatment-time and recovery-time.

The number of aberrant cells at each dish was shown at the first and the second lines. The total number of aberrant cells was shown at the third line.

Cell growth rate at each dish was shown at the first and the second lines. The average of them was shown at the third line.

DMSO: dimethyl sulfoxide, MMC: mitomycin C.

The historical control data were presented in the following table.

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Negative control

Treatment method		Frequency of cells with chromosomal aberrations (% mean±S.D.)	
		Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	1.0 ±0.72	0.6 ±0.60
	With S9 mix	1.3 ±0.70	0.6 ±0.57
24 hours continuous treatment		1.2 ±0.86	0.5 ±0.69

Treatment method		Range of frequency of cells with chromosomal aberrations (% mean±3S.D.)	
		Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	0.0 ~ 3.2	0.0 ~ 2.4
	With S9 mix	0.0 ~ 3.4	0.0 ~ 2.3
24 hours continuous treatment		0.0 ~ 3.8	0.0 ~ 2.6

When the minimum range was below 0, it was shown "0.0".

Positive control

Treatment method		Substance	Dose (µg/mL)	Frequency of cells with chromosomal aberrations (% mean±S.D.)	
				Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	MMC	0.1	63.9 ±7.36	0.5 ±0.68
	With S9 mix	CPA	6	35.0 ±11.46	0.5 ±0.60
24 hours continuous treatment		MMC	0.05	73.9 ±4.14	0.4 ±0.37

Treatment method		Range of frequency of cells with chromosomal aberrations (% mean±2S.D.)	
		Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	49.2 ~ 78.6	0.0 ~ 1.9
	With S9 mix	12.1 ~ 57.9	0.0 ~ 1.7
24 hours continuous treatment		65.6 ~ 82.2	0.0 ~ 1.1

When the minimum range was below 0, it was shown "0.0".

The incidence of aberrations at the highest concentrations tested was 6.5% without S9 and 7.0% with S9 after 6 hour treatment. These were higher than the historical control mean and range provided by the sponsor (mean: 1-1.3% and range: 0-3.4%). At these concentrations, the treatment provided approximately 50% inhibition of cell growth. Therefore, it is concluded that the results were positive. A consult regarding the positive finding of this study was sent to the CDER Genetic Toxicology Subcommittee on July 22, 2008. The subcommittee

concurs with our conclusion that this study was positive (see Appendix A).

Study title: In vivo mouse micronucleus test

Study report No: October 9, 2007

Testing Laboratory: (b) (4)

Date of study initiation: October 9, 2007

Date of study report: December 3, 2007

GLP Compliance: This study was conducted in accordance with Good Laboratory Practice Regulations of the United States Food and Drug Administration (21 CFR Part 58).

QA-report: Yes (x) No ()

Drug Batch No.:

Study Endpoint: Frequency of cells with micronucleated reticulocytes.

Methods: To examine the potential mutagenic effects of TAK-390, micronucleus test was conducted using mouse bone marrow cells. TAK-390 was given to male Crlj:CD1(ICR) mice by oral gavage at 62.5, 125, 250, 500, 1000, and 2000 mg/kg once daily on 2 consecutive days. Hydroxypropyl methylcellulose solution and cyclophosphamide monohydrate were used as negative and positive controls, respectively. All the animals in the highest dose group (2000 mg/kg) were found dead. Decrease in locomotor activity was noted in animals of the 1000 and 2000 mg/kg groups. Mice in other groups were sacrificed at 24 hours after treatment and bone marrow was collected. The frequency of micronucleated reticulocyte was determined. The result is considered positive if a significant increase in the micronucleated reticulocytes is observed dose-dependently.

Results:

- Study validation: The positive controls significantly increased the frequency of micronucleated reticulocytes.

Study outcome: TAK-390 did not significantly increase the frequency of micronucleated reticulocytes at the doses tested. The results were summarized in the following table.

Table 3 Results of micronucleus assay

Compound	Dose (mg/kg/day) ×times	Animal number	MNIEs			IEs	
			Number of IEs scored	Number	Incidence (%)	Number of erythrocytes scored	IEs/ (IEs+MEs) (%)
Negative control (1 w/v% HPMC)	0×2 ¹	10101	2000	4	0.20	1000	49.8
		10102	2000	1	0.05	1000	50.6
		10103	2000	3	0.15	1000	55.5
		10104	2000	1	0.05	1000	53.3
		10105	2000	1	0.05	1000	54.1
		(Total) (10000) (10)	Mean±SD			0.10 ± 0.07	
Test substance (TAK-390)	250×2 ¹	10401	2000	1	0.05	1000	50.0
		10402	2000	3	0.15	1000	55.3
		10403	2000	1	0.05	1000	51.8
		10404	2000	1	0.05	1000	50.3
		10405	2000	3	0.15	1000	57.0
		(Total) (10000) (9)	Mean±SD			0.09 ± 0.05	
	500×2 ¹	10501	2000	3	0.15	1000	51.0
		10502	2000	2	0.10	1000	50.5
		10503	2000	2	0.10	1000	52.5
		10504	2000	2	0.10	1000	51.9
		10505	2000	5	0.25	1000	52.4
		(Total) (10000) (14)	Mean±SD			0.14 ± 0.07	
	1000×2 ¹	10601	2000	0	0.00	1000	50.5
		10602	2000	1	0.05	1000	52.2
		10603	2000	1	0.05	1000	47.6
		10604	2000	1	0.05	1000	54.3
		10605	2000	3	0.15	1000	56.4
		(Total) (10000) (6)	Mean±SD			0.06 ± 0.05	
Positive control (CP)	40×1 ²	10801	2000	31	1.55	1000	53.8
		10802	2000	44	2.20	1000	49.6
		10803	2000	33	1.65	1000	48.6
		10804	2000	30	1.50	1000	51.0
		10805	2000	23	1.15	1000	49.1
		(Total) (10000) (161) ^{***}	Mean±SD			1.61 ± 0.38	

IEs: Immature erythrocytes, MNIEs: Micronucleated IEs, MEs: Mature erythrocytes,
HPMC: Hydroxypropyl methylcellulose, CP: Cyclophosphamide monohydrate

1. Administered twice by oral gavage at 24 hours interval.

2. Administered once by intraperitoneal injection.

3. Significantly different from the negative control (## p<0.01) by Conditional Binomial test.

Summary: The results suggest that TAK-390 was not mutagenic in this test system.

2.6.6.5 **Carcinogenicity:** Not applicable.

2.6.6.6 **Reproductive and developmental toxicology**

Effects of TAK-390 on Embryo-Fetal Development in Rabbits
(Study 250523)

Testing Laboratory: (b) (4)

Study Start and Completion Dates: February 2, 2004 and August 6, 2004

GLP and QAU Compliance Statement: Sponsor included a statement of compliance with GLP regulation and a quality assurance statement.

Animals: Kbl:NZW rabbits

Lot #M390-010

Methods: To determine the potential teratological effects, TAK-390 was given by oral gavage to pregnant rabbits at 3, 10, and 30 mg/kg/day during days 6 to 18 of gestation. Another group of pregnant rabbits received AG-1749 (lansoprazole) at 30 mg/kg/day during days 6 to 18 of gestation. Dose selection was based on the dose ranging study in non-pregnant female rabbits (study 250523P). In this study, treatment with TAK-390 and AG-1749 at 30 mg/kg/day for 5 days reduced body weight gain and food consumption. AG-1749 was also tested previously at 30 mg/kg/day in rabbits. In the current study, all animals were observed daily for clinical signs of toxicity and mortality. Body weights and food consumptions were determined. The pregnant animals were sacrificed on day 28 of gestation. Number of corpora lutea and implantation sites, live and dead fetuses, fetal and placental weights and fetal sex were recorded. All live fetuses were examined externally. Fetuses were also examined for visceral and skeletal alterations.

Results: Treatment with both TAK-390 and AG-1749 decreased fecal volume, body weight gain, and food consumption. There

were no treatment effects on the number of corpora lutea or number of implantation sites. One dam treated with AG-1749 aborted. No treatment related changes were noted on the pre-implantation and postimplantation losses, live fetuses, fetal sex ratio and weight. No clear treatment related changes on external and visceral examination were noted. However, TAK-390 at 30 mg/kg and AG-1749 at 30 mg/kg increased the incidence of unossified talus and the incidence of full supernumerary ribs. The results were summarized in the following tables.

Table 6. Necropsy findings in dams

Group mg/kg	Vehicle control	TAK-390			AG-1749
	0	3	10	30	30
Number of dams on Day 28 of pregnancy	18	17	18	19	18
Normal	18	16	18	19	18
Kidney					
Defect, left	0	1	0	0	0
Number of dams which aborted	0	0	0	0	1
Normal	-	-	-	-	1
Number of dams which delivered prematurely	0	1	0	0	0
Normal	-	1	-	-	-

Table 7. Necropsy findings in dams and fetuses (continued)

Group mg/kg	Vehicle control	TAK-390			AG-1749
	0	3	10	30	30
Number of dams	18	17	18	19	18
Mean placental weight (g)					
Male (Mean ± S.D. per dam)	5.01 ± 0.75 (17)	5.36 ± 0.70	5.15 ± 1.11	5.38 ± 1.27 (18)	5.18 ± 0.93
Female (Mean ± S.D. per dam)	4.92 ± 0.59	5.17 ± 0.71	4.82 ± 0.82 (17)	4.97 ± 1.14	5.18 ± 0.89
Number of fetuses with external abnormalities	3	0	3	0	0
Mean % ± S.D. per dam ^{d)}	2.4 ± 5.6	0.0 ± 0.0	1.9 ± 7.8	0.0 ± 0.0 W	0.0 ± 0.0
Cleft lip	0	0	3	0	0
Mean % ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	1.9 ± 7.8	0.0 ± 0.0	0.0 ± 0.0
Thoracogastroschisis	1	0	0	0	0
Mean % ± S.D. per dam	0.9 ± 3.9	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Umbilical hernia	2	0	0	0	0
Mean % ± S.D. per dam	1.5 ± 4.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0 W	0.0 ± 0.0
Acaudate	1	0	0	0	0
Mean % ± S.D. per dam	0.8 ± 3.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Number of abnormal placentae	0	0	0	0	0
Mean % ± S.D. per dam ^{e)}	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

c): (Number of fetuses with external abnormalities/number of live fetuses) × 100.

d): (Number of abnormal placentae/number of placentae examined) × 100.

Significantly different from vehicle control group (W: P<0.05 by Williams' test or Shirley-Williams test).

Figures in parentheses indicate number of dams.

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Table 8. Visceral examination of fetuses

Group mg/kg	Vehicle control	TAK-390			AG-1749
	0	3	10	30	30
Number of dams	18	17	18	19	18
Number of fetuses examined	145	134	151	145	148
Abnormalities					
Number of fetuses with abnormalities	3	0	1	0	0
Mean % ± S.D.	2.3 ± 5.5	0.0 ± 0.0	0.7 ± 2.9	0.0 ± 0.0 W	0.0 ± 0.0
Interrupted aortic arch	1	0	0	0	0
Mean % ± S.D.	0.9 ± 3.9	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Malpositioned subclavian artery	0	0	1	0	0
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.7 ± 2.9	0.0 ± 0.0	0.0 ± 0.0
Diaphragmatic hernia	1	0	0	0	0
Mean % ± S.D.	0.9 ± 3.9	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Absent kidney	1	0	0	0	0
Mean % ± S.D.	0.6 ± 2.6	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Malpositioned kidney	1	0	0	0	0
Mean % ± S.D.	0.8 ± 3.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Variations					
Number of fetuses with variations	11	9	6	10	3
Mean % ± S.D.	8.4 ± 19.5	7.9 ± 13.0	3.5 ± 7.0	7.5 ± 11.1	2.0 ± 4.8
Absent lung lobe (accessory lobe)	10	9	6	7	1
Mean % ± S.D.	7.5 ± 19.5	7.9 ± 13.0	3.5 ± 7.0	5.4 ± 10.2	0.5 ± 2.1
Abnormal lung lobation	1	1	0	0	0
Mean % ± S.D.	0.9 ± 3.9	0.7 ± 3.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Supernumerary lung lobe	0	0	0	2	1
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	1.3 ± 5.7	0.6 ± 2.4
Abnormal liver lobation	0	0	0	0	1
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 3.9
Supernumerary liver lobe	0	0	0	1	0
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.8 ± 3.3	0.0 ± 0.0
Dilated renal pelvis	0	0	0	1	0
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 3.8	0.0 ± 0.0

Significantly different from vehicle control group (W: P<0.05 by Williams' test or Shirley-Williams test).

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Table 9. Skeletal examination of fetuses

Group	Vehicle control		TAK-390			AG-1749
	0	3	10	30	30	
mg/kg	18	17	18	19	18	
Number of dams	145	134	151	145	148	
Number of fetuses examined	145	134	151	145	148	
Abnormalities						
Number of fetuses with abnormalities	4	0	6	4	1	
Mean % ± S.D.	3.1 ± 6.1	0.0 ± 0.0	3.6 ± 8.5	2.0 ± 6.6	0.5 ± 2.0	
Misshapen premaxilla	0	0	3	0	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	1.9 ± 7.8	0.0 ± 0.0	0.0 ± 0.0	
Thoracic hemivertebra	0	0	1	0	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.4	0.0 ± 0.0	0.0 ± 0.0	
Absent thoracic arch	0	0	1	0	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.6	0.0 ± 0.0	0.0 ± 0.0	
Fused thoracic arch	0	0	1	0	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.6	0.0 ± 0.0	0.0 ± 0.0	
Small thoracic arch	1	0	0	0	0	
Mean % ± S.D.	0.8 ± 3.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Fused thoracic centrum	0	0	1	1	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.6	0.5 ± 2.1	0.0 ± 0.0	
Absent lumbar vertebra	2	0	0	2	0	
Mean % ± S.D.	1.4 ± 4.1	0.0 ± 0.0	0.0 ± 0.0	1.0 ± 4.2	0.0 ± 0.0	
Absent lumbar arch	0	0	0	1	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 2.1	0.0 ± 0.0	
Fused lumbar arch	1	0	0	0	0	
Mean % ± S.D.	0.8 ± 3.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Fused lumbar centrum	0	0	0	1	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 2.1	0.0 ± 0.0	
Fused caudal vertebra	1	0	0	0	0	
Mean % ± S.D.	0.8 ± 3.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	
Fused sternebra	0	0	0	1	1	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.5	0.5 ± 2.0	
Sternumschisis	1	0	0	0	1	
Mean % ± S.D.	0.9 ± 3.9	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 2.0	
Fused rib	0	0	2	1	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	1.2 ± 3.4	0.5 ± 2.1	0.0 ± 0.0	
Branched rib	1	0	0	1	0	
Mean % ± S.D.	0.6 ± 2.6	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 2.1	0.0 ± 0.0	
Fused lumbar and sacral centrum	1	0	0	0	0	
Mean % ± S.D.	0.8 ± 3.4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	

(Continued)

Table 9. Skeletal examination of fetuses (continued)

Group	Vehicle control		TAK-390			AG-1749
	0	3	10	30	30	
mg/kg	18	17	18	19	18	
Number of dams	145	134	151	145	148	
Number of fetuses examined	145	134	151	145	148	
Variations						
Number of fetuses with variations	107	112	127	123	128	
Mean % ± S.D.	74.1 ± 33.3	83.3 ± 27.2	84.1 ± 24.0	85.6 ± 22.4	88.1 ± 18.9	
Hemicentric thoracic centrum	0	0	1	0	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 2.6	0.0 ± 0.0	0.0 ± 0.0	
Peduncular fused sternebra	0	0	1	0	0	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.7 ± 2.9	0.0 ± 0.0	0.0 ± 0.0	
Full supernumerary rib	74	95	100	105	109	
Mean % ± S.D.	52.9 ± 36.0	71.1 ± 28.4	67.3 ± 30.6	74.2 ± 27.3 W	75.1 ± 29.0	
Short supernumerary rib	44	32	42	41	30	
Mean % ± S.D.	30.3 ± 22.3	23.5 ± 17.2	25.9 ± 21.3	27.5 ± 20.5	19.6 ± 17.2	
Cervical rib	0	0	0	0	3	
Mean % ± S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	3.2 ± 8.5	

Significantly different from vehicle control group (W: P<0.05 by Williams' test or Shirley-Williams test).

(Continued)

Toxicokinetic Parameters: The results of the plasma level of the test drugs were presented in the following table.

Table 1 Toxicokinetic parameters for TAK-390 and T-168391 in female rabbits

Dose (mg/kg/day)	Analyte	Day of gestation	Female (N=5)		
			Tmax (h)	Cmax (ng/mL)	AUC _{0-24h} (ng·h/mL)
3	TAK-390	6th	0.3 (0.0)* ³	42 (38)	40 (35)
		18th	0.3 (0.0)	49 (37)	37 (32)
	T-168391	6th	- (-)	0 (0)	0 (0)
		18th	- (-)	0 (0)	0 (0)
10	TAK-390	6th	0.6 (0.4)	214 (218)	224 (161)
		18th	0.5 (0.3)	198 (203)	344 (451)
	T-168391	6th	- (-)	0 (0)	0 (0)
		18th	0.3 (-)* ¹	1 (2)	1 (1)
30	TAK-390	6th	0.4 (0.3)	1251 (1081)	1564 (1190)
		18th	0.4 (0.1)	556 (649)	519 (606)
	T-168391	6th	0.6 (0.3)* ³	12 (8)	14 (9)
		18th	0.4 (-)* ²	4 (6)	4 (6)
AG-1749 30	TAK-390	6th	0.4 (0.3)	424 (225)	718 (406)
		18th	0.6 (0.4)	108 (37)	250 (94)
	T-168391	6th	0.3 (0.1)	127 (80)	127 (92)
		18th	0.4 (0.1)	62 (38)	89 (76)

Mean (S.D.)

- : Not calculated

*¹; N=1, *²; N=2, *³; N=4 : There were animals that Tmax could not be calculated because the concentrations at all time-points were less than the quantification limit (5 ng/mL).

The plasma levels of TAK-390 were increased with dose. The S(-) enantiomer of AG-1749, T-168391, was also detected in the plasma in the high dose group of TAK 390 but the plasma level of T-168391 was lower than that of TAK 390.

In summary, TAK-390 was given by oral gavage to pregnant rabbits at 3, 10, and 30 mg/kg/day during days 6 to 18 of gestation. Another group of pregnant rabbits received AG-1749 (lansoprazole) at 30 mg/kg/day during days 6 to 18 of gestation. Treatment with both TAK-390 and AG-1749 decreased fecal volume, body weight gain, and food consumption. There were no treatment related effects on the number of corpora lutea or number of implantation sites. One dam treated with AG-1749 aborted. No

treatment related changes were noted on the pre-implantation and postimplantation losses, live fetuses, fetal sex ratio and weight. No clear treatment related changes on external and visceral examination were noted. However, both TAK-390 and AG-1749 increased the incidence of variations including unossified talus and full supernumerary ribs at dose of 30 mg/kg/day. TAK-390 was not teratogenic.

2.6.6.7 Local tolerance: Not applicable.

2.6.6.8 Special toxicology studies: Not applicable.

LABELING: The sponsor's proposed labeling is in accordance with the current Structured Product Labeling Format and consistent with the approved labeling for Lansoprazole.

1. Sponsor's Version:

8.1 Pregnancy

Pregnancy Category B. (b) (4)

As animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Evaluation: Some editorial changes are recommended.

Suggested Version:

8.1 Pregnancy

Pregnancy Category B.

A reproduction study has been conducted in rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately 9-fold the maximum recommended human dexlansoprazole dose (60 mg) based on body surface area [BSA]) and has revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole.

Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

2. Sponsor's Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m²) basis, of a 50-kg person of average height (1.46 m² BSA) given the recommended human dose of 30 mg lansoprazole per day (22.2 mg per m²). Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats (see Clinical Pharmacology(12.2)).

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day (4 to 40 times the recommended lansoprazole human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with 50 mg lansoprazole per kg per day (13 times the recommended lansoprazole human dose based on BSA) in a 1-year toxicity study.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 mg to 600 mg per kg per day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300

mg and 600 mg lansoprazole per kg per day (40 to 80 times the recommended lansoprazole human dose based on BSA) and female mice treated with 150 mg to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended lansoprazole human dose based on BSA).

Lansoprazole was negative in the Ames test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test and the rat bone marrow cell chromosomal aberration test. Lansoprazole was positive in in vitro human lymphocyte chromosomal aberration tests.

Dexlansoprazole was positive in the Ames test. In an in vitro chromosome aberration test using Chinese hamster lung cells, dexlansoprazole was judged equivocal because the percentage of affected cells increased slightly but did not reach the preset criteria for a positive response. An in vivo mouse micronucleus test was negative.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended lansoprazole human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

Evaluation: The sponsor used lansoprazole labeling to assess the carcinogenic potential and the potential effects on fertility and reproductive performance of dexlansoprazole. The approach is adequate and the information of lansoprazole is correct. However, we do not agree with the sponsor on the interpretation of the result of the in vitro chromosome aberration test with dexlansoprazole. Therefore, the sponsor should be asked to revise the genotoxic portion of the labeling for dexlansoprazole.

Suggested Version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dexlansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung

cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Lansoprazole is a gastric parietal cell (H⁺-K⁺)-ATPase inhibitor and an approved drug for treatment and maintenance use for healing and symptom relief of duodenal ulcer. TAK-390 is the R-(+)-enantiomer of lansoprazole. TAK-390MR is a modified release formulation of TAK-390. The TAK-390MR dosage form releases drug over a prolonged period of time and produces lower plasma level of the active drug. Pharmacology studies indicated that TAK-390 was more potent than the racemic lansoprazole and T-168391 (S-(-)-lansoprazole) on the inhibition of basal gastric acid secretion in rats with ID₅₀ of 1.2, 1.9, and 9.7 mg/kg for TAK-390, racemic lansoprazole, and T-168391, respectively. TAK-390, racemic lansoprazole, and T-168391 also inhibited the histamine-stimulated acid secretion with ID₅₀ of 0.4, 0.8, and 4.0 mg/kg, respectively, in rats. Both R-(+)- and S-(-)-enantiomers of lansoprazole inhibited the acid formations with IC₅₀ of 59 μM for R-(+)-enantiomer and 82 μM for S-(-) -enantiomer in isolated parietal cells from dog gastric fundic mucosa. The results suggest that the pharmacological activity of racemic lansoprazole are mainly from its R-(+)-enantiomer, TAK-390.

In the current submission, the sponsor submitted a NDA for (b) (4) Dexlansoprazole Delayed Release capsules (30, 60 (b) (4) mg) for the following indications: (1) Healing (b) (4) of all grades of erosive esophagitis (EE), (2) Maintaining healing of (b) (4) Treating (b) (4) heartburn (b) (4) associated with gastroesophageal reflux disease (GERD). In support of this NDA, the sponsor submitted the following studies: (1) pharmacology, (2) pharmacokinetics, and (3) in vitro Purkinje fiber study, (4) 3-month repeat-dose toxicity study in rats, (5) 3-month repeat-dose toxicity study in dogs, (6) genotoxicity studies including Ames tests, an in vitro chromosomal aberration test using Chinese hamster lung cells, and an in vivo mouse micronucleus test, and (7) segment II reproductive toxicity study in rabbits.

TAK-390 is orally absorbed with oral bioavailability of 2.7% in rats and 22% in dogs. The maximum plasma concentration was achieved at 0.2 hours after oral dose in rats (C_{max} = 22 ng/ml) and dogs (C_{max} = 442 ng/ml). In contrast, the modified

release formulation of TAK-390 was absorbed slowly with Tmax of 1.3-1.6 hours in rats and 2.3 hours in dogs (Tmax = 0.3 hours in rats and 1.3-1.7 hours in dogs for racemic lansoprazole). It declined quickly with plasma half life of 0.6 hours in both rats and dogs. CYP2C19 and CYP3A4 were the major metabolic enzymes for biotransformation of TAK-390, lansoprazole, and T-168391.

In the 4-week oral toxicity study in rats, Wistar rats were treated by oral gavage with TAK-390 and T-168391 at 0, 15, 50, and 150 mg/kg/day for 4 weeks. Another group of rats received racemic lansoprazole at 150 mg/kg/day by oral gavage. There were no treatment related changes in mortality, clinical signs of toxicity, ophthalmology, and urinalysis. Treatment with TAK-390 reduced terminal body weight gain by 14% in females or 20% in males at high dose of 150 mg/kg/day. The terminal body weight gain was decreased by 11% in females or 19% in males in group of racemic lansoprazole. The terminal body weight gain was also decreased by 18% in females or 15% in males in group of T-168391 (S(-) isomer). Histopathological examination revealed eosinophilic change in chief cells and vacuolization in parietal cells of the stomach in all treatment groups including TAK-390, T-168391, and racemic lansoprazole with higher incidences at high dose groups of 150 mg/kg/day. Hypertrophy of centrilobular hepatocytes was noticed in the high dose groups of TAK-390 and T-168391, and the group of racemic lansoprazole. The severity and incidence of these histopathological changes were comparable in the groups of TAK-390, T-168391, and racemic lansoprazole. The stomach was the target organ of toxicity.

In the 13-week oral toxicity study in rats, Wistar rats were treated by oral gavage with TAK-390 at 0, 5, 15, and 50 mg/kg/day for 13 weeks. Another group of rats received racemic lansoprazole at 50 mg/kg/day for 13 weeks. There were no treatment related changes in mortality, clinical signs of toxicity, body weight, ophthalmology, and urinalysis. Histopathological examination revealed eosinophilic change in chief cells of the stomach and liver hypertrophy in all treatment groups including TAK-390 and racemic lansoprazole. The stomach was the target organ of toxicity.

In the 13-week oral toxicity study in dogs, Beagle dogs were treated by oral capsule with TAK-390 at 0, 5, 15, and 50 mg/kg/day for 13 weeks. Another group of dogs received racemic lansoprazole at 50 mg/kg/day for 13 weeks. There were no treatment related changes in mortality, body weight, ophthalmology, ECG, hematology, clinical chemistry, and

urinalysis. Clinical signs of toxicity such as vomiting and soft/watery feces were noted in the treatment groups. Histopathological examination revealed vacuolation and necrosis of parietal cells of stomach in all treatment groups including lansoprazole. In the liver, bile thrombus was also noted in one male each at high dose of both TAK-390 and lansoprazole and one female each at mid dose TAK-390 and lansoprazole. The liver and stomach were the target organs of toxicity.

TAK-390 was positive in the Ames tests and in the in vitro chromosomal aberration test using Chinese hamster lung cells. TAK-390 was negative in the in vivo micronucleus test in mice.

TAK-390 was not teratogenic in the segment II reproductive toxicity study in rabbits.

The sponsor has conducted the recommended nonclinical studies with dexlansoprazole. The major target organ of toxicity was the stomach identified in the 3-month repeat-dose toxicity study in rats and dogs. The results indicated that both dexlansoprazole and lansoprazole have similar toxicity profiles. Dexlansoprazole was not teratogenic in the reproductive toxicity segment II study in rabbits. Dexlansoprazole was positive in the Ames tests and in the in vitro chromosome aberration test using Chinese hamster lung cells. These results should be included in the labeling for dexlansoprazole.

Higher incidence of cardiac ischemic events was reported in the dexlansoprazole group as compared to the placebo control group in the clinical trials with dexlansoprazole. Dexlansoprazole had no effects on the ECG and platelet count at doses up to 50 mg/kg/day in the 13-week oral toxicity study in dogs. The blood pressure was not monitored in this study. Lansoprazole had no effects on the blood pressure and heart rate at i.d. dose of 300 mg/kg in anesthetized cats and at i.d. dose of 150 mg/kg in dogs. In dogs, a continuous i.v. infusion of 1, 3 or 10 mg/kg (infusion rate of 0.067 ml/kg/min, i.e., 0.033, 0.010 and 0.333 mg/kg/min respectively) of lansoprazole increased heart rate by 14.4% and pulmonary arterial pressure by 5.9 % in 10 min of its administration. The dose of 10 mg/kg resulted in the peak plasma levels of 11.2 ug/ml (about 9 times the levels produced by a single clinical dose of 1.2 mg/kg). However, it is not known how much dexlansoprazole, the R-(+)-enantiomer of lansoprazole, was present in the dog plasma in

this study. To further investigate the potential cardiac ischemic effects of dexlansoprazole, the sponsor should be asked to conduct studies with dexlansoprazole on platelet aggregation using human peripheral platelets as a phase 4 commitment.

Recommendations:

1. From a preclinical standpoint, approval of dexlansoprazole is recommended for the proposed indications.
2. The sponsor should be asked to conduct studies with dexlansoprazole on platelet aggregation using human peripheral platelets.
3. The labeling should be revised as recommended.

Ke Zhang, Ph.D. Date
Pharmacologist, HFD-180

Comments:

Sushanta Chakder, Ph.D. Date
Acting Supervisory Pharmacologist
HFD-180

CC:
IND
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Zhang

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Appendix A: A response from the CDER Genetic Toxicology Subcommittee on pages 61-63.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DRAFT MEMORANDUM

DATE: August 8, 2008

TO: Ke Zhang, Ph.D.
Division of Gastroenterology Products

FROM: Tim Robison, Ph.D.
Co-Chair, Genetic Toxicology Subcommittee

SUBJECT: Chinese hamster lung cell chromosomal aberration assay with
Dexlansoprazole (NDA 22-287)

Participants: Mamata De (DAARP), David Jacobson-Kram (OND-IO), Martha Moore
(NCTR), Yanli Ouyang (DMIHP), and Tim Robison (DPAP)

Background: For the 6-hr treatment, incidences of chromosomal aberrations in Chinese hamster lung (CHL) cells were increased to 6.5% at 140 µg/mL TAK-390 without S9 and 7.0% at both 80 and 100 µg/mL TAK-390 with S9. The relative numbers of cells were 49.3% and 62.8 and 49.9% at these concentrations, respectively. The testing laboratory historical control mean and range of chromosomal aberrations in CHL cells were 1-1.3% and 0-3.4%, respectively.

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Table 4 Results of chromosomal aberration test of TAK-390

Substance	Dose (µg/mL)	Treatment- recovery time (hour)	S9 mix	Relative number of cells (%)	Relative Mitotic Index ^{a)} (%)	Precipitation of test substance in medium ^{b)}			Frequency of cells with aberrations (%) ^{c)}	
						Treatment start	Treatment end	Culture end	Structural aberration	Numerical aberration
DMSO	0	6-18	-	100	100	-	-	-	1.0	1.0
TAK-390	60.0	6-18	-	88.2	139.3	-	-	-	n.o.	n.o.
	80.0	6-18	-	73.3	151.4	-	-	-	n.o.	n.o.
	100	6-18	-	62.7	188.8	-	-	-	2.0	1.0
	120	6-18	-	58.3	151.4	-	-	-	2.5	2.0
	140	6-18	-	49.3	103.8	-	-	-	6.5	1.0
	160	6-18	-	46.2	70.1	-	-	-	n.o.	n.o.
	180	6-18	-	34.2	35.5	-	-	-	n.o.	n.o.
	200	6-18	-	21.9	16.9	-	-	-	n.o.	n.o.
MMC	0.1	6-18	-	ND	ND	-	-	-	67.5	0.0
DMSO	0	6-18	-	100	100	-	-	-	1.5	0.5
TAK-390	40.0	6-18	-	94.3	102.6	-	-	-	n.o.	n.o.
	60.0	6-18	-	78.4	103.3	-	-	-	1.0	1.0
	80.0	6-18	-	62.8	102.6	-	-	-	7.0	1.5
	100	6-18	-	49.9	89.6	-	-	-	7.0	3.0
	120	6-18	-	37.8	57.5	-	-	-	n.o.	n.o.
	140	6-18	-	34.0	51.0	-	-	-	n.o.	n.o.
	160	6-18	-	29.7	18.3	-	-	-	n.o.	n.o.
	180	6-18	-	23.0	15.1	-	-	-	n.o.	n.o.
	200	6-18	-	14.3	9.2	-	-	-	n.o.	n.o.
CPA	6	6-18	-	ND	ND	-	-	-	24.0	0.5
DMSO	0	24-0	-	100	100	-	-	NA	2.0	1.5
TAK-390	10.0	24-0	-	100.5	98.8	-	-	NA	n.o.	n.o.
	20.0	24-0	-	98.8	101.3	-	-	NA	n.o.	n.o.
	40.0	24-0	-	77.5	116.3	-	-	NA	1.0	0.5
	60.0	24-0	-	53.6	63.8	-	-	NA	1.0	0.0
	80.0	24-0	-	36.9	68.8	-	-	NA	9.5	1.0
	100	24-0	-	29.5	52.5	-	-	NA	n.o.	n.o.
	120	24-0	-	12.3	d)	-	-	NA	n.o.	n.o.
MMC	0.05	24-0	-	ND	ND	-	-	NA	77.0	1.0

DMSO: dimethylsulfoxide, MMC: mitomycin C, CPA: cyclophosphamide monohydrate, ND: not detected.

n.o.: not observed, NA: not applicable

a) Mitotic index was calculated by observing 1000 cells per dose.

b) Precipitation of the test substance: -, absence; +, presence

c) The frequency of cells with chromosomal aberrations was calculated by observing 200 metaphases per dose.

d) It was not calculated, since most cells died.

Question to the Committee: The reviewer judged that the CHL cell chromosomal aberration assay was positive based upon increased incidences of aberrations at the highest concentrations of the test article analyzed in the absence and presence of S9. Further, these incidences exceeded the upper end of the historical control range. The reviewer seeks concurrence from the subcommittee that the assay was positive.

Committee Discussion: The subcommittee concurs with the reviewer that the assay was positive. Observed increases after the 6 hr treatment with the test article, dexlansoprazole, in the absence and presence of S9 were relatively small, but clearly outside of the historical control range. The increase following a 24-hr treatment with 80 µg/mL in the absence of S9 occurred at a high level of cytotoxicity (36.9% relative

number of cells). It is noted that racemic lansoprazole has previously been demonstrated to be clastogenic.

The subcommittee discussed whether the sponsor should conduct an appropriate follow-up study to further assess the significance of the current finding; however, the need for such a study was considered minimal given the extensive studies performed with racemic lansoprazole to determine its genotoxic and carcinogenic potential.

Tumor findings in rodents treated with proton pump inhibitors such as lansoprazole have generally been attributed to elevated gastrin levels or other rodent-specific mechanisms.

Conclusions: The subcommittee concurs that the CHL cell chromosomal aberration assay with TAK-390 was positive.

cc:

DeM

Jacobson-KramD

MooreM

OuyangY

RobisonT

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this page is the manifestation of the electronic signature.**

/s/

Ke Zhang
12/1/2008 01:31:51 PM
PHARMACOLOGIST

Sushanta Chakder
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