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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-566

Pharmacology Review(s)

09/15/03

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21,566

Product Name: Prevacid / Lansoprazole

Sponsor: TAP Pharmaceutical Products Inc.

Indication: Prevacid i.v. infusion is indicated for the short term treatment (up to 7 days) of all grades of erosive esophagitis when patients are unable to take the oral formulation.

Division: Division of Gastrointestinal and Coagulation Drug Products

Reviewer: Ke Zhang, Ph.D.

Date: September 8, 2003

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EXECUTIVE SUMMARY**1. Recommendations**

1.1 Recommendation on approvability

From a preclinical standpoint, approval of intravenous administration of prevacid is recommended for short term treatment (up to 7 days) of all grades of erosive esophagitis when patients are unable to take the oral formulation.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendations on labeling

Sponsor should be asked to revise the labeling as recommended.

2. Summary of nonclinical findings

2.1 Pharmacologic Activity:

Lansoprazole is substituted benzimidazole and belongs to a class of antisecretory compounds. It suppresses gastric acid secretion by specific inhibition of the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell and blocks the final step of acid production. It was demonstrated that intravenous administration of lansoprazole inhibited basal gastric acid secretion at ID₅₀ of 1.67 mg/kg in rats and histamine-induced gastric acid secretion at ID₅₀ of 0.28 mg/kg in rats and 0.14 mg/kg in dogs. Inhibition of gastric acid secretion was also demonstrated following intravenous administration of lansoprazole at 30 mg/kg in humans. The suppression of acid secretion following intravenous administration was as or more effective than oral administration of lansoprazole.

The pharmacokinetic studies indicated that following intravenous administration of lansoprazole the plasma level of the unchanged drug declined quickly with t_{1/2} of 0.3 hours in rats, and t_{1/2α} of 0.6 hours and t_{1/2β} of 0.6-11 hours in dogs. In humans, the plasma level of lansoprazole decreased rapidly with a terminal t_{1/2} of ~1 hour following both oral and i.v. administrations. The metabolic patterns of lansoprazole were similar following oral and i.v. administrations in rats and dogs. Irrespective of the route of administration (oral or

i.v.), approximately 26-32% and 64-69% radioactivity were excreted in the urine and feces, respectively, over 72 hours in both rats and dogs. Intravenous administration of lansoprazole produces higher systemic exposure as compared to the oral administration in both animals and humans.

2.2 Toxicological Findings

The results of the acute i.v. toxicity studies indicated that the minimal lethal dose of lansoprazole (in saline) was 218 mg/kg in male mice and 167 mg/kg for female rats. Following clinical signs of toxicity were noted in both mice and rats: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait.

The results of the 13-week i.v. toxicity studies indicated that the stomach was the target organ of toxicity in both rats and dogs. Histopathological examination revealed eosinophilic chief cells, hypertrophy and hyperplasia of the chief cells and microaggregation of the ECL cells in the stomach in rats, and atrophy, vacuolation and necrosis of the parietal cells, and hyperplasia of the foveolar and neck region of the stomach. In addition, thymus (atrophy of the thymus), and liver (hypertrophy of the centrilobular hepatocytes) were also identified as target organs of toxicity in rats.

Treatment with lansoprazole did not affect fertility and mating performance of the male and females rats at i.v. doses up to 30 mg/kg/day in the Segment I Fertility and general reproductive performance studies in rats.

Lansoprazole was not teratogenic at i.v. doses up to 30 mg/kg/day in the Segment II teratology study in rats and rabbits.

Treatment with lansoprazole did not produce any adverse effects on perinatal and postnatal development at i.v. doses up to 30 mg/kg/day in the Segment III study in rats.

In vitro hemolytic studies revealed no hemolytic potential in rabbit blood at lansoprazole concentration of 6 mg/ml (1:1 mixture). Intravenous injection of lansoprazole (6 mg/ml) produced mild edema and inflammatory cell infiltration at the injection site in rabbits.

3. Administrative:

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

Comments:

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

CC:

NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Choudary

HFD-180/Dr. Zhang

HFD-048/Dr. Viswanathan

R/D Init.: J. Choudary 8/29/03

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PHARMACOLOGY/TOXICOLOGY REVIEW**3.1 INTRODUCTION AND DRUG HISTORY**

NDA number: 21,566

Review number: 01

Sequence number/date/type of submission: December 23, 2002

Information to sponsor: Yes () No (x)

Sponsor and/or agent: TAP Pharmaceutical Products Inc.

Manufacturer for drug substance:

[

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Reviewer name: Ke Zhang

Division name: Division of Gastrointestinal and Coagulation

Drug Products

HFD #: 180

Review completion date: September 8, 2003

Drug:

Trade name: Prevacid i.v. for injection

Generic name: Lansoprazole

Code name: A-65006 / AG-1749

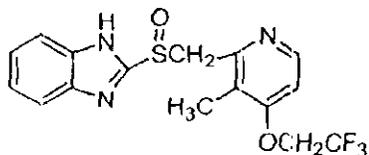
Chemical name:

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

CAS registry number: 103577-45-3

Molecular formula/molecular weight: C₁₆H₁₄F₃N₃O₂S and 369.36

Structure:

Relevant INDs/NDAs/DMFs: IND 41,938 (lansoprazole injection),
IND [] and NDA 20,406 (lansoprazole capsules).Drug class: Parietal cell (H⁺-K⁺)-ATPase inhibitor / Proton pump inhibitor.

Indication: Prevacid i.v. infusion (30 mg over 30 minutes, daily) is indicated for the short term treatment (up to 7 days) of all grades of erosive esophagitis when patients are unable to take the oral formulation.

Clinical formulation:

Table 2.0a Composition of Lansoprazole for Injection

Ingredients	Compendial Reference	Amount per vial ^b	Function	Amount for a Full-Scale Lot
Lansoprazole ^a	Regulatory Specification	30 mg	Active	[
Mannitol	USP	60 mg	↓	
Meglumine	USP	10 mg		
Sodium hydroxide ^a	NF	3.45 mg		
Water for Injection	USP	N/A ^d		
[]	↓]

a

[

b

c

d

]

Source: TAP-02-000943-1.0, TAP-02-001093-1.0

Route of administration: I.v. Injection.

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

Studies reviewed within this submission:

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study #	Lot #	lab	Page #
Pharmacology				8
Acute Toxicity:				8-16
Acute i.v. toxicity studies in mice and rats	A-29-899	Z338201	1	
Acute i.v. toxicity study in mice	A-29-2175	Z338709	1	
Acute i.v. toxicity study in mice - Supplemental study	A-29-2177	Z338709	1	
Acute i.v. toxicity study in rats	A-29-2174	Z338709	1	
Acute i.v. toxicity study in rats - Supplemental study	A-29-2176	Z338709	1	
Acute i.v. toxicity study with degraded AG-1749 in rats	A-29-2178	Z338721	1	
Acute i.v. toxicity studies in dogs	A-29-2143	Z338704 Z338707 Z3387T01 Z930519	1	
Subacute/subchronic/chronic Toxicity:				17-42
1-week i.v. toxicity study in rats	A-29-765	M610-016	1	
2-week i.v. toxicity study in rats	A-29-504	M610-016	1	
4-week i.v. toxicity study in rats	A-29-805	M610-018	1	
4-week i.v. toxicity study in rats	A-29-767	M610-018	1	
13-week i.v. toxicity study in rats	A-29-2142	Z338705	1	
1-week i.v. toxicity study in dogs	A-29-1300	M610-018	1	
2-week i.v. toxicity study in dogs	A-29-505	M610-016	1	
4-week i.v. toxicity study in dogs	A-29-806	M610-018	1	
13-week i.v. toxicity study in dogs	A-29-2075	Z338T01 Z338T07 Z338T08 Z338T09	2	
13-week i.v. toxicity study in dogs	A-29-1861 A-29-2184	M610-050	3	

1 = []
 2 = []
 3 = []

Type of Study	Study #	Lot #	lab	Page #
<u>Reproductive Toxicity:</u>				43-56
I.V. Segment I fertility and general reproductive performance study in male rats	A-29-1773	Z338201 Z338202	1	
I.V. Segment I fertility and general reproductive performance study in male and female rats	A-29-2046	Z338707 Z338708 Z338709 Z338711	1	
I.V. Segment II Teratology study in rats	A-29-1783	Z338201	1	
I.V. Segment II Teratology study in rats	A-29-2065	Z338704	1	
I.V. Segment II Teratology study in rabbits	A-29-2066	Z338704	1	
I.V. Segment III perinatal and postnatal study in rats	A-29-2067	Z338704	1	
<u>Special Toxicity:</u>				56-60
Hemolytic potential of lansoprazole in rats	A-29-902 A-29-1782			
Hemolytic potential of lansoprazole in rabbits	A-29-901 A-29-1781			
Hemolytic potential of lansoprazole in rabbits	A-29-2717			
Hemolytic potential of lansoprazole in rabbits	A-29-02992			
I.v. irritation study in rabbits	A-29-2718			
I.v. tolerance study in rabbits	A-29-02995			
I.v. irritation study in rabbits	A-29-900 A-29-1780			
Paravenous irritation study in rabbits	A-29-1818			

The cardiovascular pharmacology study in anesthetized dogs, intravenous toxicity studies including acute i.v. toxicity studies in mice and rats, 2-week and 4-week i.v. toxicity studies in rats and dogs, and 13-week i.v. toxicity studies in rats and dogs, i.v. Segment I fertility and general reproductive performance studies in rats, i.v. Segment II teratology studies in rats and rabbit, and i.v. Segment III perinatal and postnatal study in rats were submitted to IND 41,938 and NDA 20,406. These studies were reviewed in IND 41,938 on September 2, 1993 (initial submission), on June 24, 1997 (Amendments 005, 007, and 015), and in NDA 20,406 on January 9, 1995. The pharmacology reviews of these studies are incorporated in the appropriate portion of the present review.

Studies not reviewed within this submission:

All mutagenicity studies submitted in this submission were not reviewed since these studies were not specifically for the intravenous administration. These studies were reviewed previously in NDA 20,406 on January 9, 1995.

3.2 PHARMACOLOGY

3.2.4 Safety pharmacology

Cardiovascular pharmacology:

Cardiovascular pharmacology study in anesthetized dogs following intravenous infusion of [] (study # ['90/125)

A continuous 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 produced an 14.4% increase in heart rate and a slight increase of 5.9 % in pulmonary arterial pressure in 10 min of its administration. A 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).

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:

3.4.2 Single-dose toxicity

Study title: Acute i.v. toxicity studies in mice and rats

Key study findings: The highest non-lethal i.v. dose (in polyethylene glycol 400) was 58 mg/kg/day for both male and female mice and 44 mg/kg for male rats and 58 mg/kg for female rats. The minimal lethal i.v. dose was 75 mg/kg for both male and female mice and 58 mg/kg for male rats and 75 mg/kg for female rats. Decreased activity, respiratory depression, flattened posture, ataxia, and hyporeactivity were noted in both mice and rats. Almost all deaths occurred within 3 minutes after injection. The clinical signs of toxicity disappeared 30 minutes after dosing in the survived animals.

Study no.: A-29-899

Volume #, and page #: Volume 1.8, page 001

Methods: The acute i.v. toxicity of Lansoprazole was studied in mice and rats. Drug was dissolved in the "PEG vehicle" pH 10.3-10.5 (for details of vehicle see formulation). The rate of injection was 0.1-0.5 ml/min for mice and 1.0-1.5 ml/min for rats. The volume of administration in mice and rats were 14.7-32.7 ml/kg. No vehicle control was included in the study. All animals were observed for toxic signs and mortality daily for 14 days. At the end of observation period all animals were sacrificed and necropsied.

Results:

Acute I.V. Toxicity Study of Lansoprazole in Mice and Rats

Species (strain)	No/Sex/ Dose Group	Dose (mg/kg)	LD ₅₀ (mg/kg)		Highest Non-Lethal Dose	
			Male	Female	Male	Female
Mice (Jcl: ICR)	5	44, 58, 75, 98	80.1	75.7	58	58
Rats (Jcl: Wistar)	5	44, 58, 75, 98	69.3	71.9	44	58

The signs of toxicity in mice and rats were similar. These signs included decreased activity, respiratory depression, flattened posture, ataxia and hyporeactivity. Most deaths occurred within 30 min. after drug administration. The LD₅₀ values for male and female mice were 80.1 and 75.7 mg/kg respectively. The LD₅₀ values for male and female rats were 69.3 and 71.9 mg/kg respectively. The highest no-lethal dose in mice (both sexes) and female rats was 58 mg/kg and 44 mg/kg in male rats.

Study title: Intravenous single dose toxicity study of AG-1749 for injection in mice

Key study findings: Mice were given AG-1749 (in Polyethylene glycol 400) intravenously at 58, 75, 98, and 128 mg/kg. The minimal lethal dose was 75 mg/kg in males and 128 mg/kg in females. The deaths occurred within 2 minutes after injection. The non-lethal dose was 58 mg/kg for males and 98 mg/kg for females. Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, and ataxia gait.

Study no: A-29-2175

Volume # 1.8 and page # 001

Conducting laboratory and location: []

Date of study initiation: April 11, 1995

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Lot # Z338709

Formulation/vehicle: Polyethylene glycol 400

Methods:

Dosing:

Species/strain: Jcl:ICR mice

#/sex/group or time point (main study): 5/sex/group

Satellite groups used for toxicokinetics or recovery:

Age: 6 weeks old

Weight: 32.1-37.9 g for males and 26.6-31.2 g for females.

Doses in administered units: 58, 75, 98, and 128 mg/kg.

Route, form, volume, and infusion rate: I.v. injection

Observations and times:

Clinical signs: daily for 14 days.

Body weights: before dosing, and on days 1, 2, 7, and 14.

Gross pathology: After death or at termination.

Results:

Mortality: One male in 75 mg/kg group, 3 males in 98 mg/kg, and all males and 1 female in 128 mg/kg group.

Clinical signs: Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, and ataxia gait. The severity of these clinical signs of toxicity were dose related.

Body weights: No changes were noted in the animals that survived to the termination.

Gross pathology: necrosis at the injection site was observed in a male each in 58 mg/kg and 98 mg/kg groups.

Study title: Intravenous single dose toxicity study of AG-1749 for injection in mice -Supplemental study-

Key study findings: Mice were given AG-1749 (in Saline) intravenously at 98, 128, 167, and 218 mg/kg. The minimal lethal dose was 218 mg/kg in males. The deaths occurred within 2 minutes after injection. The non-lethal dose was 167 mg/kg for males and 218 mg/kg for females. Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait, tonic convulsion and decreased body temperature.

Study no: A-29-2177

Volume # 1.8 and page # 001

Conducting laboratory and location: C - J

Date of study initiation: April 20, 1995

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Lot # Z338709

Formulation/vehicle: Saline

Methods:

Dosing:

Species/strain: Jcl:ICR mice

#/sex/group or time point (main study): 5/sex/group

Satellite groups used for toxicokinetics or recovery:

Age: 6 weeks old

Weight: 30.1-37.4 g for males and 25.1-29.7 g for females.

Doses in administered units: 98, 128, 167, and 218 mg/kg.

Route, form, volume, and infusion rate: I.v. injection

Observations and times:

Clinical signs: daily for 14 days.

Body weights: before dosing, and on days 1, 2, 7, and 14.

Gross pathology: After death or at termination.

Results:

Mortality: Three male in 218 mg/kg group. No death occurred in the female groups.

Clinical signs: Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, and ataxia gait in all treatment groups. In addition, tonic convulsion and decreased body temperature were noted in 128 mg/kg group or higher. The severity of these clinical signs of toxicity were dose related.

Body weights: No changes were noted in the animals that survived to the termination.

Gross pathology: Necrosis, swelling, and incrustation at the injection site were observed in all treatment groups.

Study title: Intravenous single dose toxicity study of AG-1749 for injection in rats

Key study findings: Rats were given AG-1749 (in Polyethylene glycol 400) intravenously at 44, 58, 75, 98, and 128 mg/kg. The minimal lethal dose was 58 mg/kg for males and 75 mg/kg for

females. The deaths occurred within 15-30 minutes after injection. The non-lethal dose was 44 mg/kg for males and 58 mg/kg for females. Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait, and ptosis.

Study no: A-29-2174

Volume # 1.8 and page # 001

Conducting laboratory and location: [J,TD

Date of study initiation: April 11, 1995

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Lot # Z338709

Formulation/vehicle: Polyethylene glyco 400

Methods:

Dosing:

Species/strain: Jcl:Wistar rats

#/sex/group or time point (main study): 5/sex/group

Satellite groups used for toxicokinetics or recovery:

Age: 6 weeks old

Weight: 148.1-172.4 g for males and 117.7-136.5 g for females.

Doses in administered units: 44, 58, 75, 98, and 128 mg/kg.

Route, form, volume, and infusion rate: I.v. injection

Observations and times:

Clinical signs: daily for 14 days.

Body weights: before dosing, and on days 1, 2, 7, and 14.

Gross pathology: After death or at termination.

Results:

Mortality: One male in 58 mg/kg group, 3 females in 75 mg/kg, 2 males and 2 females in 98 mg/kg, and all animals in 128 mg/kg group.

Clinical signs: Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait, ptosis in all treatment groups. The severity of these clinical signs of toxicity were dose related.

Body weights: No changes were noted in the animals that survived to the termination.

Gross pathology: Necrosis at the injection site was observed in one male in 98 mg/kg group. Dark red discoloration

of the lungs and foamy fluid in the trachea were observed in the animals that died.

Study title: Intravenous single dose toxicity study of AG-1749 for injection in rats - Supplemental Study -

Key study findings: Rats were given AG-1749 (in Saline) intravenously at 75, 98, 128, and 167 mg/kg. The minimal lethal dose was 167 mg/kg for females. The death occurred within 1 minutes after injection. The non-lethal dose was 167 mg/kg for males and 128 mg/kg for females. Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait, and ptosis.

Study no: A-29-2176

Volume # 1.8 and page # 001

Conducting laboratory and location: []

Date of study initiation: April 20, 1995

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Lot # Z338709

Formulation/vehicle: Saline

Methods:

Dosing:

Species/strain: Jcl:Wistar rats

#/sex/group or time point (main study): 5/sex/group

Satellite groups used for toxicokinetics or recovery:

Age: 6 weeks old

Weight: 160.8-185.7 g for males and 122.4-144.9 g for females.

Doses in administered units: 75, 98, 128, and 167 mg/kg.

Route, form, volume, and infusion rate: I.v. injection

Observations and times:

Clinical signs: daily for 14 days.

Body weights: before dosing, and on days 1, 2, 7, and 14.

Gross pathology: After death or at termination.

Results:

Mortality: One female in 167 mg/kg group. Another female in 128 mg/kg was found dead 7 days after the injection. The death of the female was not considered treatment related.

Clinical signs: Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration,

depression of touch-escape response, flattened posture or lying on side, ataxia gait, ptosis in all treatment groups. The severity of these clinical signs of toxicity were dose related.

Body weights: No changes were noted in the animals that survived to the termination.

Gross pathology: Incrustation at the injection site was observed in males in all treatment groups. Dark red discoloration of the lungs was observed in the female that died in 167 mg/kg group.

Study title: Intravenous single dose toxicity study of Degraded AG-1749 for injection in rats

Key study findings: Rats were given degraded AG-1749 (in Polyethylene glycol 400) intravenously at 44, 58, 75, 98, and 128 mg/kg. The minimal lethal dose was 58 mg/kg for males and 75 mg/kg for females. The deaths occurred within 15 minutes after injection. The non-lethal dose was 44 mg/kg for males and 58 mg/kg for females. Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait, and ptosis. Some of the clinical signs of toxicity disappeared within 2 hours after dosing. The results were similar to those observed with the non-degraded AG-1749.

Study no: A-29-2178

Volume # 1.8 and page # 001

Conducting laboratory and location: []

Date of study initiation: August 16, 1995

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Lot # Z338721

Formulation/vehicle: Polyethylene glyco 400

Methods:

Dosing:

Species/strain: Jcl:Wistar rats

#/sex/group or time point (main study): 5/sex/group

Satellite groups used for toxicokinetics or recovery:

Age: 6 weeks old

Weight: 131.9-152.7 g for males and 96.0-114.5 g for females.

Doses in administered units: 44, 58, 75, 98, and 128 mg/kg.

Route, form, volume, and infusion rate: I.v. injection

Observations and times:

Clinical signs: daily for 14 days.

Body weights: before dosing, and on days 1, 2, 7, and 14.

Gross pathology: After death or at termination.

Results:

Mortality: One male in 58 mg/kg group, 1 male and 1 female in 75 mg/kg, 3 males and 4 females in 98 mg/kg, and all males in 128 mg/kg group.

Clinical signs: Following clinical signs of toxicity were noted: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait, ptosis in all treatment groups. The severity of these clinical signs of toxicity were dose related.

Body weights: No changes were noted in the animals that survived to the termination.

Gross pathology: Dark red discoloration of the lungs, nasal discharge and foamy fluid in the trachea were observed in the animals that died.

Study title: Intravenous escalating dose acute toxicity study of AG-1749 for injection in dogs

Key study findings: Dogs were given AG-1749 (in Polyethylene glycol 400) intravenously at 30, 60, and 120 mg/kg. Each dose was given to the same 2 males and 2 females with 3-4 days between each dose. Dogs were observed for 14 days after final dose. There were no deaths. The non-lethal dose was 120 mg/kg for males and females. Following clinical signs of toxicity were noted: decrease in locomotor activity, retching, vomiting, increased muscle tone, decreased startle response, miosis, diarrhea, flaccidity of the nictitating membrane, tremor, convulsion, ptosis and salivation. Most of the clinical signs of toxicity disappeared within 24 hours after dosing.

Study no: A-29-2143

Volume # 1.8 and page # 001

Conducting laboratory and location: [-]

Date of study initiation: October 21, 1994

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: Lot # Z3387T01, Z930519, Z338704, Z338707

Formulation/vehicle: Polyethylene glyco 400

Methods:

Dosing:

Species/strain: Beagle dogs
#/sex/group or time point (main study): 2/sex/group
Satellite groups used for toxicokinetics or recovery:
Age: 12 months old
Weight: 9.8-11.8 kg for males and 9.7-12.2 kg for females.
Doses in administered units: 30, 60, and 120 mg/kg. Each dose was given to the same 2 males and 2 females with 3-4 days between each dose.
Route, form, volume, and infusion rate: I.v. injection

Observations and times:

Clinical signs: daily for 14 days after the final dose.
Body weights: before dosing, and 7 and 14 days after 120 mg/kg dose.
Food Consumption: Daily.
Hematology and clinical chemistry: before and after dosing for low and mid dose groups. Before dosing and on days 1, 7, and 14 days after 120 mg/kg dose.

Results:

Mortality: There were no deaths in this study.
Clinical signs: There were no treatment related changes at 30 mg/kg. Ataxic gait, tremor and flaccidity of the nictitating membrane, salivation, retching, and diarrhea were noted at 60 mg/kg. Following clinical signs of toxicity were noted at 120 mg/kg: decrease in locomotor activity, retching, vomiting, increased muscle tone, decreased startle response, miosis, diarrhea, flaccidity of the nictitating membrane, tremor, convulsion, ptosis and salivation.
Body weights: No changes were noted.
Food Consumption: No treatment related changes were observed.
Hematology: There were no treatment related changes.
Clinical Chemistry: There were no treatment related changes.

3.4.3 Repeat-dose toxicity

RAT:

Study title: 2-week i.v. toxicity study in rats

Key study findings: Lansoprazole was given to rats intravenously at 0, 1, 3, and 10 mg/kg/day for 2 weeks. The high dose of 10 mg/kg/day was no effect dose.

Study no.: A-29-504

Volume #, and page #: Volume 9, page 001

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Testing Laboratories: C

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Study Started: February 1, 1989

Study Completed: June 30, 1989

GLP Requirements: Not mentioned

Animals: Jcl: Wistar rats (6 weeks old; males: 151-167g and females: 122-136g)

Drug Batch No.: M610-016

Placebo Batch No.: ZR655-05

Methods: In this study dose selection was based on preliminary 1-week i.v. toxicity study in rats in which doses of 0 (vehicle: mannitol, pH 12-12.1), 30, 60 and 100 mg/kg/day were used. Bradypnea, decreased activity, and necrosis at the injection sites were seen in mid and high dose treated rats. Three out of 4 males died in high dose group within 4 days. At 60 mg/kg, thymus and prostate weights were decreased by 36% and 31% respectively, when compared to their respective control values. Histopathological examination revealed atrophy of the thymus and s.c. hemorrhage at the injection site in 60 and 100 mg/kg treated rats. The no effect dose in this study was 30 mg/kg/day. Based on these findings 30 mg/kg/day was chosen as the highest dose for subsequent 4-week I.V. toxicity study.

In the main study groups of 5 male and 5 female rats were given I.V. injection of Lansoprazole at daily doses of 0 (saline), 0 (vehicle: "mannitol", pH 10.5), 1, 3 and 10 mg/kg/day for 2 weeks. The volume of administration was fixed at 5 ml/kg/day (4 ml/min). The highest tested dose level in this study is about 33 times the intended human dose (15 mg/person or about 0.3 mg/kg). All animals were observed daily for clinical signs and mortality. Body weights were recorded on days 0, 3, 7, 10 and 14 of the study and food intakes were recorded weekly. Ophthalmoscopic examinations were performed on all control and high dose treated rats once pretest and once during week 1 of the study. All animals were starved for about 20 hr. after the last dose, and blood samples were collected from abdominal aorta for hematological and serum chemistry tests. Four-hour urine samples

were also collected between 21-24 hr. after dosing for urinalysis. All surviving animals were sacrificed at the end of the study period and subject to complete necropsy and histopathological examinations.

Results:

1. Observed Effects: None
2. Mortality: None
3. Body Weight/Food Consumption/Water Consumption: No treatment related effects were seen.
4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen.
5. Vital Signs/Physical Examination/Ophthalmic Examination: No treatment related effects were seen.
6. Organ Weights: Stomach weights were increased by 16-23% in all treated rats (reflection of pharmacologic effect).
7. Gross Pathology: No treatment related effects were seen.
8. Histopathology: No treatment related effects were seen.

The data indicated that the highest tested dose was no effect dose in this study.

REVIEWER'S ADDENDUM:

A part of materials and methods from the review of the above study was deleted because it described the 4-week subacute toxicity study as the basis of the dose selection. This was incorrect and inaccurate.

Addendum: The preliminary 1-week intravenous toxicity study in rats (study #A-29-765) described in the method section was designed to determine the dose range for the 4-week i.v. toxicity study in rats (see below).

Study title: 4-week i.v. toxicity study in rats

Key study findings: Lansoprazole was given to rats intravenously at 0, 3, 10, and 30 mg/kg/day for 4 weeks. The high dose of 30 mg/kg/day was no effect dose.

Study no.: A-29-805

Volume #, and page #: Volume 9, page 0

Testing Laboratories: [

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Study Started: January 12, 1990Study Completed: June 27, 1990GLP Requirements: A Statement of Compliance with GLP regulation was included.Animals: []: Wistar Rats (6 weeks old, males: 132-151g and females: 106-124g)Drug Batch No.: M610-018Placebo Batch No.: 004

Methods: Groups of rats (10/sex/group) were given I.V. injection of Lansoprazole at daily doses of 0 (saline), 0 (vehicle: "mannitol" pH 10.6-10.8), 3, 10 and 30 mg/kg/day for 4 weeks. The dose selection was based on 2-weeks I.V. toxicity study (see above). The rate of administration was 4 ml/min. The volume of administration for saline, vehicle and high dose groups was 10 ml/kg/day. The volumes of administration in low and mid dose groups were 1 and 3.3 ml/kg/day respectively. All animals were observed for clinical signs and mortality daily. Body weights were recorded on day 1, 3, and 7 of the study and twice a week thereafter. Food intakes were recorded weekly. Ophthalmoscopic examinations were performed on 5 rats/sex/group once pretest and on day 24 (before dosing) of the study. All animals were starved for about 20 hr. after the last dose and blood samples were collected from abdominal aorta for hematological and serum chemistry tests. On day 25 the 4-hr. urine samples were also collected from 5 rats/sex/group for urinalysis. All surviving rats were sacrificed at the end of the study period and subjected to complete necropsy. Histopathological examinations were performed on all tissues from control, vehicle control and high dose group. Additionally, liver, kidney, stomach and injection site from all rats in low and mid dose groups were also examined microscopically. In this study hepatic drug metabolizing enzymes (amino-N-demethylase and aniline hydroxylase) activities were also monitored.

Results:

1. **Observed Effects:** No treatment related effects were seen.
2. **Mortality:** None
3. **Body Weight/Food Consumption/Water Consumption:** Body weight gains in high dose treated males were decreased by 14% and this was accompanied with a reduction of 6% in food consumptions.
4. **Hematology/Coagulation/Bone Marrow:** No treatment related effects were seen.
5. **Blood Chemistry/Urinalysis:** At 30 mg/kg/day, serum cholesterol levels were increased by 13% compared to the control values. Plasma T₄ and T₃ levels were normal. No treatment related effects were seen in urinalysis.
6. **Vital Signs/Physical Examination/Ophthalmic Examination:** No treatment related effects were seen.
7. **Organ Weights:** Stomach weights were increased by 10-15% in all treated rats compared to the control values. In high dose group, thymus weights were decreased by 21% and 30% in males and females respectively compared to their respective control values.
8. **Gross Pathology:** Thymus atrophy was evident in high dose treated rats (males = 5/10 and females = 7/10).
9. **Histopathology:** Eosinophilia and hypertrophy of the chief cells of the stomach were seen in treated rats (males: control = 0/10, vehicle control = 0/10, low dose = 1/10, mid dose = 2/10 and high dose = 3/10; females: control = 0/10, vehicle control = 0/10, low dose = 0/10, mid dose = 1/10 and high dose = 1/10). No other treatment related abnormality was observed (including liver).
10. **Activity of Hepatic Drug-Metabolizing Enzymes:** In high dose treated male rats, hepatic aminopyrine-N-demethylase and aniline hydroxylase activities were increased by 21% and 13% respectively when compared to their respective control values.

In this study the data indicated that 10 mg/kg/day was the no effect dose.

Addendum: There was a supplementary 4-week i.v. dose ranging study in rats (A-29-767, Volume 1.9). In this study, AG-1749 was given intravenously to male rats at 0 and 60 mg/kg/day for 4 week. The results indicated that one treated animal was found dead and another treated animal was sacrificed due to severe damage at the injection sites. The study was terminated on day 26 due to severe lesions at the injection site. Following toxicity were observed in the treated animals: bradypnea,

hypoactivity, decreased body weight gain and food consumption, and inflammation at the injection sites.

Study title: 13-week i.v. toxicity study in rats

Key study findings: Lansoprazole was given to rats intravenously at 0, 3, 10, 30, and 60 mg/kg/day for 13 weeks. Histopathological examination revealed eosinophilic chief cells, hypertrophy and hyperplasia of the chief cells and microaggregation of the ECL cells in the stomach, atrophy of the thymus, and hypertrophy of the centrilobular hepatocytes in the treated animals, suggesting that the stomach, thymus, and liver were the target organs of toxicity. Lansoprazole was tolerated at dose of 10 mg/kg/day.

Study no.: A-29-2142

Volume #, and page #: Volume 1.10, page 001

Testing Laboratories: C

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Study Started: March 14, 1994

Study Completed: December 19, 1994

GLP Requirements: A Statement of Compliance with GLP Regulations was included.

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Animals: Six weeks old [] Wistar rats (males: 169-194 g and females: 119-140 g).

Drug Batch No.: 2338705

Methods: In this study dose selection was based on preliminary 4-week i.v. toxicity study, report of which was not submitted to us. According to the sponsor a dose of 60 mg/kg/day produced decrease locomotor activity, suppression of body weight gain and atrophic changes in thymus, and a dose of 30 mg/kg/day produced decrease locomotor activity in males and atrophic changes in thymus of females. Based on these findings sponsor selected 3, 10, 30 and 60 mg/kg/day dose levels for the present study.

Groups of rats (15/sex/group) were given I.V. injection of Lansoprazole at daily doses of 0 (saline), 0 (vehicle: "mannitol" pH 10-11), 3, 10, 30 and 60 mg/kg/day (the corresponding volumes of administration were 10, 10, 0.5, 1.67, 5 and 10 ml/kg/day respectively) for 91 days. Five rats/sex/group were used as satellite animals for monitoring drug levels in plasma. All animals were observed daily for clinical signs and mortality. Body weights were recorded twice weekly during the first 4 weeks of the study and weekly thereafter. Food consumptions were recorded weekly. Ophthalmoscopic examinations were performed on all rats at pretest and on day 81 of the study. Just before sacrifice blood samples were collected from abdominal aorta for hematological and serum chemistry tests. Blood samples were also collected from satellite animals at pretest, 5, 15, 30, min. and 1, 2 and 4 hr after drug administration on days 1, 28 and 91 of the study to monitor drug levels in plasma. Eighteen hr. urine samples were also collected from 5 rats/sex/group on day 24/25 and 88 of the study for urinalysis. At the end of study period all animals were sacrificed and subjected to complete necropsy and histopathological examinations. Additionally, liver samples from 5 rats/sex/group were used to monitor cytochrome p-450 content and hepatic drug metabolizing enzymes (amino-N-demethylase and aniline hydroxylase) activities.

Results:

1. **Observed Effects:** Irregular respiration, decreased locomotor activity and prone position were seen in high dose treated rats.
2. **Mortality:** One male and one female from high dose group and 1 male from satellite high dose group died immediately after the first dose due to dyspnea. These animals were replaced by naive rats. During the course of study 3 males in high dose group died immediately after dosing (day 24, 58 and 84 respectively) due to dyspnea.

3. Body Weight/Food Consumption/Water Consumption: At the end of treatment period, body weight gains were reduced by 17.5% and 16.3% in high dose treated males and females respectively, when compared to vehicle control values. Body weight gains in 30 mg/kg/day treated females were also decreased by 7.6% compared to vehicle control values. In high dose treated males, food consumptions were significantly decreased throughout the study period (about 12%). No consistent effect on food intakes were seen in treated females.

4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen.

5. Blood Chemistry/Urinalysis: Serum creatinine kinase activities were increased by 71% and 70% in females treated with 30 and 60 mg/kg/day dose levels respectively, when compared to vehicle control values. In high dose treated males, serum cholesterol levels were increased by 22% and in high dose treated females lactic dehydrogenase activity was increased by 62% when compared to their respective vehicle control values.

6. Vital Signs/Physical Examination/Ophthalmic Examination: No treatment related effects were seen.

7. Organ Weights: Thymus weights were decreased by 21% and 69% in males, and 33% and 50% in females at 30 and 60 mg/kg/day dose levels respectively, when compared to the vehicle control values. Additionally, in high dose treated males, relative weights of lung, liver, kidney, adrenals and testes were increased by 12%, 14%, 15%, 25% and 13% respectively, when compared to the vehicle control values. In high dose treated females, relative weight of heart, lungs, liver, kidneys and adrenals were increased by 11%, 19%, 23%, 15% and 16% respectively compared to the control values.

8. Gross Pathology: Atrophy of the thymus was seen in mid (males = 1/10 and females = 1/10) and high (males = 7/7 and females = 6/10) dose treated rats.

9. Histopathology: Eosinophilic chief cells hypertrophy and hyperplasia of the chief cells, and microaggregation of ECL cells were seen in the stomach of rats treated with ≥ 3 mg/kg/day. Atrophy of the thymus was seen in rats treated with ≥ 30 mg/kg/day. Hypertrophy of the centrilobular hepatocytes were seen at 60 mg/kg/day dose levels. The incidences of the above mentioned findings were as follows:

Histopathological Findings in Rats							
Organs/ Findings	Sex (M/F)	Control	Vehicle	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day	60 mg/kg/day
# Examined		10	10	10	10	10	10
Stomach/							
Eosinophilic Chief Cells	M	0	0	10	10	10	9
	F	0	0	5	7	9	9
Hypertrophy of the chief cells	M	0	0	7	6	8	8
	F	0	0	2	3	5	6
Hyperplasia of the chief cells	M	0	0	1	1	1	6
	F	0	0	1	1	1	2
Microaggregation of ECL cells	M	0	0	4	4	4	3
	F	0	0	2	4	3	5
Thymus/							
Atrophy	M	0	0	2	3	6	8
	F	0	0	0	0	2	10
Liver/							
Centrilobular hypertrophy of hepatocytes	M	0	0	0	0	0	2
	F	0	0	0	0	0	9

10. Hepatic Drug Metabolizing Enzyme Activities: At 60 mg/kg/day, pentoxyresorufin-o-dealkylase (PROD: related to CYP2B1/2 isoform of P450) and ethoxyresorfin-o-dealkylase (EROD: related to CYP1A1 isoform of P450) activities in liver were increased by 1308% and 105% in males, and 1850% and 33% in females respectively, when compared to their respective control values. Data indicated that the drug is inducer of CYP2B1/2 and CYP1A1 isoforms of P450 in rats. In liver of 60 mg/kg/day treated rats, the total cytochrome-P450 content was increased by 22-26% (both sexes).

11. Drug Levels in Plasma: Plasma levels of the drug increased dose dependently. The data indicated that AUC in females were significantly higher than that seen in males. Irrespective of sex, plasma levels on day 91 were higher than that seen on day 1 of the study.

Table 22 Pharmacokinetic parameters of AG-1749 in rats

Dose (mg/kg)	No. of dosing	Male (N=5)	Female (N=5)	Total (N=10)
		AUC 0-4h ($\mu\text{g} \cdot \text{h}/\text{ml}$)	AUC 0-4h ($\mu\text{g} \cdot \text{h}/\text{ml}$)	AUC 0-4h ($\mu\text{g} \cdot \text{h}/\text{ml}$)
3	1 st	0.48 \pm 0.04	0.73 \pm 0.05	0.61 \pm 0.14
	28th	0.56 \pm 0.09	1.02 \pm 0.11	0.79 \pm 0.26
	91th*	0.91 \pm 0.09	1.37 \pm 0.06	1.14 \pm 0.26
10	1 st	1.97 \pm 0.10	2.71 \pm 0.11	2.34 \pm 0.40
	28th	2.18 \pm 0.18	3.45 \pm 0.19	2.81 \pm 0.69
	91th*	3.26 \pm 0.44	5.23 \pm 0.12	4.25 \pm 1.12
30	1 st	7.47 \pm 0.86	11.47 \pm 0.52	9.47 \pm 2.21
	28th	8.31 \pm 1.87	16.52 \pm 0.84	12.42 \pm 4.54
	91th*	13.31 \pm 1.09	24.48 \pm 1.62	18.90 \pm 6.24
60	1 st	21.21 \pm 2.13	30.38 \pm 4.15	25.80 \pm 5.75
	28th	24.19 \pm 3.17	42.01 \pm 3.95	33.10 \pm 9.98
	91th*	27.47 \pm 0.71	46.22 \pm 1.33	36.85 \pm 10.32

Mean \pm S.D. (*: Male, Female; N=3, Total: N=6).

In this study the target organs of toxicities were stomach, thymus and liver. The lowest tested dose (10 mg/kg/day) can be considered as well tolerated dose since it only produced histopathological changes in the stomach which is related to the pharmacological activity of the drug.

DOG:

Study title: 2-week i.v. toxicity study in dogs

Key study findings: Lansoprazole was given to dogs intravenously at 0, 1, 3, and 10 mg/kg/day for 2 weeks. The high dose of 10 mg/kg/day was no effect dose.

Study no.: A-29-505

Volume #, and page #: Volume 1.11, page 001

Testing Laboratories: [

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Study Started: February 23, 1989

Study Completed: June 30, 1989

GLP Requirements: Not mentioned

Animals: Beagle Dogs (6 months old; males: 8.6-11.8 kg and females: 8.4-10.1 kg)

Drug Batch No.: M 610-016

Placebo Batch No.: ZR 655-05

Methods: Groups of 3 male and 3 female dogs were given I.V. injection of Lansoprazole at daily doses of 0 (saline), 0 (vehicle): "mannitol" pH 11.0), 1, 3 and 10 mg/kg/day for 14 days. The volume of administration was 2 ml/kg/day for control, vehicle control and high dose group, and 0.2 ml/kg and 0.6 ml/kg

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were the volume of administration in low and mid dose respectively. The injection rate was fixed at 3 ml/min. The highest tested dose level in this study is about 33 times the intended human dose (15 mg/person or about 0.3 mg/kg). All animals were observed daily for clinical signs and mortality. Body weights were recorded weekly and food intakes were recorded daily. ECG were monitored during pretest and 1 hr. after the 9th dose. Blood samples were collected from cephalic vein during pretest, day 7 and day 14 of the study for hematological and serum chemistry tests. Twenty-four hr. urine samples were collected during pretest and day 3 of the study for urinalysis. At the end of the study period all dogs were sacrificed and subjected to complete necropsy and histopathological examinations.

Results:

1. Observed Effects: None
2. Mortality: None
3. Body Weight/Food Consumption/Water Consumption: No treatment related effects were seen.
4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen.
5. Blood Chemistry/Urinalysis: No treatment related effects were seen.
6. Vital Signs/Physical Examination/ECG: No treatment related effects were seen.
7. Organ Weights: No treatment related effects were seen.
8. Gross Pathology: No treatment related effects were seen.
9. Histopathology: Hemorrhage, connective tissue proliferation and inflammatory cell infiltration were seen at the injection site in vehicle treated and drug treated dogs.

The data indicated that the highest tested dose was no effect dose in this study.

Study title: 4-week i.v. toxicity study in dogs

Key study findings: Lansoprazole was given to dogs intravenously at 0, 3, 10, and 30 mg/kg/day for 4 weeks. The histopathological examination revealed that hypertrophy and single cell necrosis of parietal cells in the stomach, suggesting that the stomach was the target organs of toxicity. The dose of 3 mg/kg/day was no effect dose.

Study no.: A-29-806

Volume #, and page #: Volume 1.11, page 001

Testing Laboratories: [

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Study Started: January 12, 1990

Study Completed: July 17, 1990

GLP Requirements: A Statement of Compliance with GLP Regulations was included.

Animals: Beagle Dogs (9 months old, males: 10.1-13.7 kg and females: 9.1-11.1 kg.

Drug Batch No.: M 610-018

Placebo Batch No.: 004

Methods: In this study dose selection was based on preliminary 1-week i.v. toxicity study in dogs (# A-29-1300) in which doses of 0 (saline), 0 (vehicle: mannitol, pH 12.0-12.1), 30 and 100 mg/kg/day were used. Emesis, salivation, ptosis, flaccid nictating membrane and decreased activity was seen in high dose treated dogs. Hemorrhage and edema at the injection sites were seen in vehicle and drug treated dogs and these changes were severe in high dose treated dogs. High dose treated female dogs lost 5% of its weight by the end of 7 days of treatment. Necrosis of the chief cells and parietal cells in stomach was observed in high dose treated dogs. Thrombus in the lungs were seen in males treated with 30 and 100 mg/kg/day dose levels. Sponsor concluded that 100 mg/kg/day would exceed the maximum tolerated dose. Hence, 30 mg/kg/day was chosen as the highest dose for subsequent 4-week I.V. toxicity study.

In the main study groups of 3 male and 3 female dogs were given I.V. injection of Lansoprazole at daily doses of 0 (saline), 0 (vehicle: "mannitol" pH 10.9-11.1), 3, 10 and 30 mg/kg/day for 4 weeks. The volume of administration was 6 ml/kg/day for control, vehicle control and high dose group, and 0.6 and 2 ml/kg were the volume of administration in low and mid dose respectively. The injection rate was fixed at 3 ml/min. All animals were observed daily for clinical signs and mortality. Body weights were recorded weekly and food consumption were recorded daily. ECG recording and ophthalmoscopic examinations were performed on all dogs at pretest. On week 4 ECG recordings were also obtained from all saline, control, vehicle control and high dose treated dogs before and after administration of the dose. On week 4, ophthalmoscopic examinations were also done on these dogs. Blood samples were collected from cephalic vein during pretest, day 7, 14 and 29 of the study for hematological and serum chemistry tests. Eighteen hr. urine samples were collected during pretest and on day 27 of the study for urinalysis. At the end of study

period all animals were sacrificed and subjected to complete necropsy and histopathological examinations. In this study hepatic drug-metabolizing enzymes (amino-N-demethylase and aniline hydroxylase) activities were also monitored.

Results:

1. Observed Effects: Swelling at the injection site and reddening of the mucous membranes were seen in 1/3 males and 1/3 females of high dose group.
2. Mortality: None
3. Body Weight/Food Consumption/Water Consumption: No treatment related effects were seen.
4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen.
5. Blood Chemistry/Urinalysis: No treatment related effects were seen.
6. Vital Signs/Physical Examination/Ophthalmic Examination: No treatment related effects were seen.
7. Organ Weights: In high dose treated females, liver weights were increased by 36% compared to the control value. Additionally, liver weight was also increased (39%) in 1 out of 3 high dose treated male dogs.
8. Gross Pathology: At the injection sites moderate to marked hemorrhage, s.c. edema were seen in high dose treated dogs.
9. Histopathology: At the injection sites S.C. hemorrhage, edema/thrombus were seen in all treated dogs and severity was dose related. Vacuolization in the parietal cells of stomach was seen in treated dogs (males: saline control = 0/3, vehicle control = 0/3, low dose = 3/3, mid dose = 3/3 and high dose = 3/3; females: saline control = 0/3, vehicle control = 0/3, low dose = 2/3, mid dose = 3/3 and high dose = 3/3). Single cell necrosis of the parietal cells (males: saline control = 0/3, vehicle control = 0/3, low dose = 0/3, mid dose = 2/3 and high dose = 2/3; females: saline control = 0/3, vehicle control = 0/3, low dose = 0/3, mid dose = 2/3 and high dose = 3/3) were seen in treated dogs. Additionally, 1/3 male and 1/3 females each of mid and high dose group had hypertrophy of the parietal cells. Single cell necrosis of chief cells were also seen in 1/3 mid dose treated male dogs and in 1/3 males and 1/3 females of high dose group.

In this study target organ of toxicity was stomach. The lowest dose (3 mg/kg/day) can be considered a no effect dose.

Study title: 13-week i.v. toxicity study in dogs

Key study findings: Lansoprazole was given to dogs intravenously at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Histopathological examination revealed inflammation and fibrosis of the vein wall and perivenous tissues in all treated dogs and the severity was dose related. Hyperplasia of the glandular neck and foveolar region of the fundic glands and atrophy of the parietal cells of the stomach were found in the treated dogs.

Study no.: A-29-1861 / A-29-2184

Volume #, and page #: Volume 1.12, page 001

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Testing Laboratories: [J.

Study Started: June 1, 1992

Study Completed: November 6, 1992

GLP Requirements: A Statement of Compliance with GLP Regulations was included.

Animals: Beagle Dogs (8-11 months old, males: 8.6-12.8 kg and females: 7.8-10.8 kg).

Drug Batch No.: M 610-050

Placebo Batch No.: TWN 6417 and TWL 7417

Methods: Groups of 4 male and 4 female dogs were given I.V. injection of Lansoprazole at daily doses of 0 (vehicle: "mannitol" pH 10.9-11.1), 3, 10 and 30 mg/kg/day for 13 weeks. The volume of administration was 6 ml/kg/day for control, vehicle control and high dose group, and 0.6 and 2 ml/kg were the volume of administration in low and mid dose respectively. The injection rate was fixed at 2 ml/min. All animals were observed 3 times daily for clinical signs and mortality. Body weights, food and water consumptions were recorded weekly. Ophthalmoscopic examinations were performed on all dogs at pretest and twice during treatment period (week 4 and 13). Blood samples were collected from cephalic vein during pretest and twice during treatment period (week 6 and 13) for hematological and serum chemistry tests. Eighteen hr. urine samples were also collected during above mentioned period for urinalysis. Additionally, blood samples were also collected from all dogs before drug administration and 5, 10, 15 and 30 min and 1, 2 and 4 hr after drug administration on days 1, 7, 14, 21, 49 and 90 of the study for measuring plasma drug levels. Plasma gastrin levels were also determined in all animals at 4 hr after dosing on day 1, 7, 14, 21, 49 and 90 of the study. On day 90 of the study plasma gastrin levels were also measured at 2 and 6 hr after drug administration. At the end of study period all

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animals were sacrificed and subjected to complete necropsy and histopathological examinations. In this study hepatic drug-metabolizing enzymes activities were also monitored and livers (2/sex/group) were examined under electron microscope.

Results:

1. Observed Effects: Two out of 4 males and 2 out of 4 females in high dose group were diagnosed to have Idiopathic Necrotizing Arteritis Syndrome (beagle pain syndrome) which according to sponsor was not related to the treatment. These dogs consumed less food, showed decreased spontaneous activity and one female and one male become emaciated from week 5/7 of the study. Results from these 4 affected dogs were excluded from statistical analysis. Swelling at the injection sites were seen in 1/4 males and 1/4 females of mid dose group and in 1/4 female of high dose group.
2. Mortality: None
3. Body Weight/Food Consumption/Water Consumption: No treatment related effects were seen except significant loss in body weight, decreased food and water intakes were evident in dogs (males: # 25 and # 27 and females: # 30 and # 32) of high dose group which were diagnosed to have Idiopathic Necrotizing Arteritis Syndrome.
4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen. Significant decreases in number of red cells (37-40%), hematocrit (38-46%) and hemoglobin (42-49%) and increases in WBC (174-200%) were seen in dogs (males: # 25 and # 27 and females: # 30 and # 32) of high dose group which were diagnosed to have Idiopathic Necrotizing Arteritis Syndrome, when compared to the pretest values.
5. Blood Chemistry/Urinalysis: No treatment related effects were seen. Significant increases in serum alkaline phosphatase activities (males 540% and females 95% over baseline values) and serum total bilirubin (males 14% and females 16%; compared to pretest values), and decreases in serum albumin/globulin ratios (males 57% and females 49%; compared to pretest values) and serum creatinine levels (males 41% and females 51%; compared to pretest values) were seen in dogs (males: # 25 and # 27 and females: # 30 and # 32) of high dose group which were diagnosed to have Idiopathic Necrotizing Arteritis Syndrome.
6. Vital Signs/Physical Examination/Ophthalmic Examination: No treatment related effects were seen.

7. Organ Weights: In high dose treated females, relative weights of liver, kidneys and adrenals were increased by 20%, 14% and 14% respectively when compared to their respective control values. Additionally, relative weights of various organs (lungs, liver, kidneys and adrenals etc) were increased in dogs having Idiopathic Necrotizing Arteritis Syndrome.

8. Gross Pathology: At the injection sites slight s.c. edema were seen in 1/4 males (# 27) and 1/4 females (#29) of high dose group. One male dog of high dose group (#25) had enlarged liver, bilateral scarring along with hemorrhage in cortex of kidney and another female dog of high dose group (#30) had discoloration of cardiac muscle and spleen, thinning of left ventricle wall, yellowish aorta wall, yellowish white nodule on the surface of spleen, scarring in kidney cortex. Both dogs (# 25 & # 30) were diagnosed to have Idiopathic Necrotizing Arteritis Syndrome.

9. Histopathology: Inflammation and fibrosis of the vein wall and perivenous tissues and intimal thickening were seen in all treated dogs and severity was dose related. Venous thrombosis (occlusive recanalized) were seen in mid and high dose treated dogs. Histopathological changes in various organs (aorta, lung, thyroid, thymus, esophagus, duodenum, jejunum, stomach, ileum, liver, spleen, heart, kidneys, mediastinal adipose tissue and bone marrow) consistent with Idiopathic Necrotizing Arteritis Syndrome were seen in 4 affected dogs of high dose group (males: # 25 and # 27 and females: # 30 and # 32). No histological changes ("hypertrophic or hyperplastic") were seen in gastric fundus of any dog.

10. Electron Microscopic Examination: Electron microscopic examination of liver revealed dilation of Disse's space, deposition of microfibrils in Disse's space, atrophy of hepatocytes and vesicularization of smooth endoplasmic reticulum in hepatocytes in dog # 25 (high dosed male with Idiopathic Necrotizing Arteritis Syndrome) and # 30 (high dosed female with Idiopathic Necrotizing Arteritis Syndrome). Additionally, increased number of lipid droplets in hepatocytes were also seen in dog # 30.

11. Plasma Drug Levels: Plasma drug levels increased with increasing dosages.

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Plasma Levels of AG-1749

Day	Sex	AUC (mcg.h/ml)		
		Low Dose, (n=4)	Mid Dose (n=4)	High Dose* (n=2)
1	M	3.35 ± 1.19	11.00 ± 1.90	38.10
	F	3.68 ± 0.77	12.32 ± 4.78	34.10
7	M	2.57 ± 0.92	6.11 ± 1.63	14.35
	F	2.24 ± 0.47	4.98 ± 2.03	14.98
14	M	2.28 ± 0.91	4.65 ± 1.32	10.02
	F	1.84 ± 0.54	4.26 ± 0.84	13.06
21	M	2.34 ± 0.74	4.52 ± 1.37	10.87
	F	1.70 ± 0.11	4.40 ± 0.65	12.95
49	M	2.53 ± 1.10	4.42 ± 0.62	10.62
	F	1.83 ± 0.84	4.31 ± 0.57	11.12
90	M	2.09 ± 0.61	6.26 ± 2.12	11.75
	F	2.00 ± 0.47	4.45 ± 0.62	10.82

* = mean of two dogs

12. Plasma Gastrin Levels: Plasma gastrin levels were highly erratic and no conclusion can be made.

Table 11 Plasma gastrin level (pg/ml)

Group	Animal No	Day	Time (hours)								
			0	1	14	21	49	90	90	90	
Control	1 2 3 4										
		Mean	126.5	119.6	128.5	140.0	132.3	106.0	177.7	176.5	
		±S.D.	36.5	24.2	9.5	17.7	30.7	14.9	73.6	42.2	
	AG-1749	9									
1 (mg/kg)	10 11 12										
		Mean	128.8	228.7	127.8	246.7	187.7	246.4	190.9	223.5	
		±S.D.	28.7	149.0	24.5	188.4	86.3	265.0	104.8	98.3	
	AG-1749	17									
10 (mg/kg)	18 19 20										
		Mean	207.7	296.1	181.0	292.0	513.8	375.0	422.9	283.4	
		±S.D.	131.4	271.6	425.0	317.2	585.3	290.2	111.2	116.0	
	AG-1749	26									
30 (mg/kg)	28										
	Mean	153.7	129.6	643.5	504.9	769.4	550.6	426.6	487.4		

Not significantly different from the control

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Table 11 (Continued)

Female		Day	6	7	14	21	49	90
Group	Animal No.	Tunc (hQwr)	4	4	4	4	4	4
Control	5	[
	6							
	7							
	8							
	Mean							
± S.D.	16.1	48.1	29.6	24.0	32.7	11.6	37.1	22.0
AG-1749 3 (mg/kg)	13	[
	14							
	15							
	16							
	Mean							
± S.D.	13.6	123.4	196.0	119.6	424.7	86.3	96.1	35.6
AG-1749 10 (mg/kg)	21	[
	22							
	23							
	24							
	Mean							
± S.D.	168.8	179.0	1019.4	31.7	2003.6	13.9	65.8	145.6
AG-1749 10 (mg/kg)	29	[
	31							
	Mean							

Not significantly different from the control.

13. Hepatic Drug-metabolizing Enzyme Induction: Drug had no statistically significant effects on hepatic drug-metabolizing enzyme activities.

Table 9 Hepatic drug-metabolizing enzyme activity Male

Parameter	control	AG-1749		
	(0mg/kg)	(3mg/kg)	(10mg/kg)	(30mg/kg)
Body weight (kg)	11.13 ± 1.22 (1.00)	11.15 ± 1.47 (1.00)	11.45 ± 1.29 (1.03)	11.80 (1.06)
Liver weight (g)	301.63 ± 25.92 (1.00)	310.48 ± 17.25 (1.03)	314.78 ± 14.06 (1.11)	348.20 (1.15)
Liver weight/body weight (g/kg)	27.073 ± 3.874 (1.00)	28.198 ± 3.815 (1.03)	29.471 ± 2.995 (1.08)	29.590 (1.08)
Microsomal protein content (mg/g liver)	38.32 ± 1.93 (1.00)	33.56 ± 1.80 (0.88)	34.84 ± 4.76 (0.91)	31.09 (0.81)
Cytochrome P-450 content (nmol/mg protein)	0.206 ± 0.074 (1.00)	0.192 ± 0.098 (0.93)	0.151 ± 0.074 (0.73)	0.187 (0.91)
Cytochrome b5 content (nmol/mg protein)	0.586 ± 0.189 (1.00)	0.756 ± 0.265 (1.29)	0.718 ± 0.298 (1.23)	0.645 (1.10)
Aminopyrine N-demethylase activity (nmol/min/mg protein)	4.395 ± 0.446 (1.00)	4.945 ± 1.437 (1.13)	4.118 ± 0.943 (0.94)	6.995 (1.39)
Aniline hydroxylase activity (nmol/min/mg protein)	0.100 ± 0.053 (1.00)	0.072 ± 0.008 (0.72)	0.058 ± 0.008 (0.58)	0.052 (0.52)
p-Nitroanisole O-demethylase activity (nmol/min/mg protein)	1.468 ± 0.075 (1.00)	1.728 ± 0.583 (1.18)	1.618 ± 0.189 (1.10)	1.130 (0.77)
p-Nitrophenyl glucuronyltransferase activity (nmol/min/mg protein)	3.45 ± 0.165 (1.00)	3.355 ± 0.309 (0.97)	3.767 ± 0.606 (1.09)	4.436 (1.29)

Data are expressed as the mean values ± S.D. of four animals in the 3 and 10 mg/kg groups and as the mean values of two animals in the 30 mg/kg group. Figures in parentheses are expressed as the ratio of drug treatment relative to control. Not significantly different from the control.

Addendum: Re evaluation of the stomach slides revealed hyperplasia of the glandular neck and foveolar region of the

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fundic glands and atrophy of the parietal cells of the stomach in the treated dogs.

Study title: 13-week i.v. toxicity study in dogs

Key study findings: Lansoprazole was given to dogs intravenously at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Histopathological examination revealed atrophy, vacuolation and necrosis of the parietal cells, and hyperplasia of the foveolar and neck region of the stomach were observed in all treated dogs. These alterations were more severe in the high dose group. The stomach was the target organ of toxicity.

Study no.: A-29-2075

Volume #, and page #: Volume 1.13, page 001

In the Amendment # 001, dated 6/28/93, sponsor submitted the results of 13-week i.v. toxicity study in dogs (report # A-29-1861). In 13-week i.v. toxicity study in dogs, doses of 3, 10 and 30 mg/kg/day were used. Two out of 4 males and 2 out of 4 females in high dose group were diagnosed to have Idiopathic Necrotizing Arteritis Syndrome (beagle pain syndrome) which according to sponsor was not related to the treatment. These dogs consumed less food, showed decreased spontaneous activity and one female and one male become emaciated from week 5/7 of the study. Results from these 4 affected dogs were excluded from statistical analysis. In this study target organ of toxicity was not identified. Inflammation and fibrosis of the vein wall and perivenous tissues, intimal thickening and venous thrombosis were seen in mid and high dose treated dogs. The lowest dose (3 mg/kg/day) was the no effect dose. The highest tested dose (30 mg/kg/day) was considered as well tolerated dose since it only

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produced increased relative weights of liver (20%), kidneys (14%), adrenals (14%) and venous thrombosis at the injection sites in high dose treated females. No histopathological abnormalities were seen when stomach slides were stained with hematoxylin-eosin. On page 13 of Amendment # 001 dated 6/28/93 (volume 2.1) sponsor indicated that there were no hypertrophic or hyperplastic changes in the argyrophil or argentaffin cells in any group (for detail see review dated 9/6/93). Sponsor reevaluated the stomach slides and reported the results in a revised final report (# A-29-2184, dated 1/9/96). Revised report indicated that in treated dogs, hyperplasia of the glandular neck and foveolar region of the fundic glands and atrophy of the parietal cells were seen. Additionally severity of single cell or focal necrosis of the parietal cells in the stomach and incidence of vacuolated parietal cells increased in high dose treated dogs.

Present study (report # A-29-2075) is a repeat of the earlier submitted study (# A-29-1861). Study # A-29-1861 was performed at [] -

Testing Laboratories: []

].

Study Started: February 9, 1994

Study Completed: September 13, 1994

GLP Requirements: A Statement of Compliance with GLP Regulations was included.

Animals: Beagle Dogs (12-14 months old, males: 7.90-12.65 kg and females: 7.70-10.45 kg).

Drug Batch No.: Z338T01, Z338T07, Z338T08 and Z338T09.

Vehicle Batch No.: Z338506.

Methods: Groups of 3 male and 3 female dogs were given I.V. injection of Lansoprazole at daily doses of 0 (control: normal saline), 0 (vehicle control: polyethylene glycol 400, HCl and water pH 10.9-11.1), 3, 10 and 30 mg/kg/day for 13 weeks. The volume of administration was 5 ml/kg/day for saline control, vehicle control and high dose groups, and 0.5 and 1.7 ml/kg were the volume of administration in low and mid dose respectively. The injection rate was fixed at 1 ml/min. All animals were observed 2 times daily for clinical signs and mortality. Body weights, food and water consumptions were recorded weekly. Ophthalmoscopic examinations were performed on all dogs at pretest and during week 13 of the study. ECG recordings were

done on all dogs at pretest and during weeks 4 and 13 of the study. Blood samples were collected from jugular vein during pretest and twice during treatment period (week 4 and 13) for hematological and serum chemistry tests. Urine samples were also collected during above mentioned period for urinalysis. Additionally, blood samples were also collected from all dogs before drug administration, immediately after dosing and 15 and 30 min and 1, 2 and 4 hr after drug administration on days 3, 15, 50 and 91 of the study for measuring plasma drug levels. Plasma gastrin levels were also determined in all animals at pretest and immediately after dosing on day 3, 15, 50 and 91 of the study. At the end of study period all animals were sacrificed and subjected to complete necropsy and histopathological examinations. In this study hepatic drug-metabolizing enzymes activities were also monitored.

Results:

1. Observed Effects: No treatment related effects were seen. Unlike the earlier study (# A-29-1861), "there was no evidence of beagle pain syndrome in any dog".
2. Mortality: One female from mid dose group (#4137) died on day 40 of the study. The cause of death was strangulated hernia and considered not to be treatment related.
3. Body Weight/Food Consumption/Water Consumption: No treatment related effects were seen.
4. Hematology/Coagulation/Bone Marrow: No treatment related effects were seen.
5. Blood Chemistry/Urinalysis: No treatment related effects were seen.
6. Vital Signs/Physical Examination/Ophthalmic Examination/ECG: No treatment related effects were seen.
7. Organ Weights: No treatment related effects were seen except ovaries weights were increased by 82% in high dose treated females.
8. Gross Pathology: No treatment related effects were seen.
9. Histopathology: Atrophy, vacuolation and necrosis of the parietal cells, and hyperplasia of the foveolar and neck region of the stomach were seen in all treated dogs. The severity of above findings were slightly higher in the high dose group than in other treated groups.

10. Plasma Drug Levels: Plasma drug levels increased with increasing dosages. There was evidence of accumulation with time and 4 hr post dosing the levels were below detection limit.

Groups	Sex (M/F)	Mean Plasma Levels (ug/ml) Immediately After Dosing			
		Day 3	Day 15	Day 50	Day 90
Low Dose	M	3.9	3.1	4.6	5.6
	F	3.8	3.6	5.0	5.3
Mid Dose	M	9.4	10.8	10.4	12.2
	F	8.9	6.9	9.1	7.5
High Dose	M	17.1	16.4	14.8	12.9
	F	22.3	17.2	13.1	13.1

11. Plasma Gastrin Levels: Plasma gastrin levels were highly erratic and no conclusion can be made.

TABLE 7
Group mean serum gastrin concentrations (pg/mL)

Group/Sex	Mean SD (n)	Control		I-33326				
		Saline	Vehicle	Group Level (mg/kg/day)				
		1	2	3	4	5	6	
		0	0	3	4	10	30	
		Occasion						
		Pre-dose	Day 3	Day 15	Day 50	Day 90		
1M	Mean SD (n)	66 23.6	36 4.6	51 5.0	54 17.9	44 17.2		
2M	Mean SD (n)	53 24.0	47 13.1	38 9.2	56 22.2	49 19.4		
3M	Mean SD (n)	-	77 15.4	68 23.4	67 25.0	63 50.7		
4M	Mean SD (n)	-	59 32.0	64 38.2	64 32.0	106 97.1		
5M	Mean SD (n)	54 6.1	72 55.5	57 15.5	67 16.7	132 96.5		
	Statistics	S1	S2	S3	S4	S5		
1F	Mean SD (n)	45 15.5	38 2.6	33 6.0	37 3.6	36 4.0		
2F	Mean SD (n)	40 4.6	29*** 1.7	36 2.5	41 6.1	31 4.2		
3F	Mean SD (n)	60 19.6	117 85.3	112 83.6	174 103.4	180 87.9		
4F	Mean SD (n)	56 27.1	81 51.5	133 70.1	55	77		
5F	Mean SD (n)	-	47 12.7	38 1.0	52*** 4.9	45*** 3.5		
	Statistics	S1	S2	S3	S4	S5		

1 excluded from statistical analysis. The number in parenthesis refers to the control group used for the comparison.
 While probabilities for control group versus treated group are subject to Bonferroni adjustments.
 S1 = Pooled variance t test
 S2 = Separate variance t test
 - mean and SD not calculated
 * p=0.05
 ** p=0.01
 *** p=0.001

12. **Hepatic Drug-metabolizing Enzyme Induction:** Drug had no statistically significant effects on hepatic microsomal protein and total cytochrome P450 contents or on the activities of ethoxycoumarine-o-dealkylase (ECOD), pentoxyresorufin-o-dealkylase (PROD), testosterone hydroxylase and UDP-glucuronyl transferase (UDPGT). However, ethoxyresorufin-o-dealkylase (EROD) activities were significantly increased in treated dogs (males: up to 4.5 fold and females: up to 10.4 fold), which indicates that the drug is inducer of CYP1A1 in beagle dogs.

Effects on Drug Metabolizing Enzymes						
Parameters	Sex (M/F)	Saline Control	Vehicle Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Microsomal Protein (mg/g liver)	M	15.9±2.1	16.4±1.3	22.0±1.3	20.1*	20.4±4.8
	F	19.0±2.5	17.3±1.2	21.6±1.9	20.8*	20.2±1.3
Cytochrome P450 (nmol/mg prot.)	M	0.35±0.05	0.45±0.08	0.47±0.07	0.54*	0.50±0.08
	F	0.47±0.13	0.48±0.10	0.58±0.18	0.60*	0.80±0.13
ECOD (nmole/mg prot.)	M	4.0±1.2	3.2±0.5	3.4±0.6	3.6*	3.1±0.8
	F	3.9±0.3	4.1±1.1	4.7±0.8	4.5*	4.5±0.4
PROD (pmole/mg prot.)	M	25.3±5.1	18.6±11.6	25.3±1.6	32.6*	20.1±3.2
	F	22.1±9.8	19.8±8.9	35.6±24.4	33.6*	33.3±10.2
16 α Hydroxy-testosterone (nmole/mg prot.)	M	0.55±0.39	0.56±0.16	0.55±0.40	0.61±0.26	0.42±0.22
	F	0.51±0.09	0.56±0.17	0.40±0.04	0.64*	0.35±0.04
UDPGT (nmo.e/mg prot.)	M	27.5±2.1	26.3±8.9	22.0±5.1	31.21*	24.4±10.8
	F	31.6*	30.4±9.1	25.5±1.6	24.4*	26.0±1.9
EROD (pmole/mg prot.)	M	94±18	64±39	297±11	323*	428*
	F	42*	91±44	251*	423*	440±12

* = Mean of two determinations.

In this study target organ of toxicity was stomach. Induction of hepatic drug metabolizing enzyme (EROD: CYP1A1 isoform of P450) was seen at all dose levels. The highest tested dose (30 mg/kg/day) can be considered as well tolerated dose since it only produced histopathological changes in the stomach which is related to the pharmacological activity of the drug.

3.4.6. Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: I.v. Segment I. Fertility and general reproductive performance study in male rats

Key study findings: Male rats were given lansoprazole intravenously at 0, 3, 10, and 30 mg/kg/day for 9 weeks before mating and throughout the mating phase and until they were sacrificed. The results indicated that treatment with lansoprazole did not affect fertility and mating performance of the male rats at intravenous doses up to 30 mg/kg/day.

Study no.: A-29-1773

Volume # 1.15, and page #: 001

Testing Laboratories: [

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Dates Study Started and Completed: May 16, 1991 and December 1992

GLP Requirements: Not mentioned

Animals: Jcl: Wistar rats (males: 7 week old, 190-234g; females 11 week old, 183-222g)

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Drug Batch No.: Z 338201 & Z 338202 (each vial contained 30 mg of AG-1749, 3.7 mg of NaOH, 10 mg of malumine and 60 mg of mannitol)

Vehicle: PEG formulation (adjusted to pH 10-11 with 0.1 NaOH)

Methods: In this study male rats (10/group) were given I.V. daily doses of 0 (saline), 0 (vehicle: "PEG formulation"), 3, 10 and 30 mg/kg/day of Lansoprazole. Male rats were treated for 9 weeks prior to mating and throughout the mating phase and until they were sacrificed (total 13 weeks of treatment). The volume of administration was 10 ml/kg and rate of administration was 2 ml/min. The dose selection was based on 4-week I.V. toxicity study (see above). Treated rats were mated with untreated females (9-10/group). All animals were observed at least once a day. Body weight of male rats were recorded weekly and pregnant females were weighed on days 0, 6, 13, 18 and 20 of gestation. Food consumption in males were recorded weekly. The mating performance and fertility of both sexes were evaluated. Males were necropsied after 13 weeks of treatment. Testis, epididymides, seminal vesicles and ventral prostate were weighed. On day 20 of gestation all dams were sacrificed and examined for number of corpora lutea, the number of implants, the number of dead or resorbed fetuses and number of live fetuses. The live fetuses were weighed and sexed. Live fetuses were examined for external abnormalities.

Results: Two high dose treated males died on day 38 and 71 of the study just after drug administration. The cause of death was considered not to be treatment related. Decreased locomotor activity was seen in 1/10 high dose treated rats. Body weight gains were reduced by 14% in high dose treated male rats compared to vehicle control values. Lansoprazole up to 30 mg/kg/day had no abnormal effects on fertility and mating performance of treated males. The number of corpora lutea, pre- and post-implantation losses, number of live fetuses, weights of fetuses and sex ratios were comparable in all groups. In this study dose selection was adequate and 30 mg/kg/day is the maximum tolerated dose in this species.

Study title: I.v. Segment I. Fertility and general reproductive performance study in rats

Key study findings: Rats (males and females) were given lansoprazole intravenously at 0, 3, 10, and 30 mg/kg/day. Males were treated for 9 weeks before mating and throughout the mating phase and until they were sacrificed. Females were treated for 2 weeks before mating, throughout mating, and until day 7 of gestation. The results indicated that treatment with lansoprazole did not affect fertility and mating performance of the male and females rats at intravenous doses up to 30 mg/kg/day.

Study no.: A-29-2046
Volume # 1.15, and page #: 001

Sponsor has earlier submitted the results of i.v. Segment I. fertility and general reproductive performance study in male rats (reporting # A-29-1773: 0, 3, 10 and 30 mg/kg/day) in which highest tested dose had no abnormal effects on the fertility and mating performance of males (for detail see review dated September 6, 1993).

Testing Laboratories: [

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Study Started: December 24, 1993

Study Completed: August 25, 1994

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Jcl: Wistar rats (males: 6 weeks old, 146-159 g and females: 11 weeks old, 192-210 g).

Drug Batch No.: Z338707, Z338708, Z338709 and Z338711.

Methods: Groups of rats (22/group) were given i.v. doses of 0 (saline), 0 (vehicle: polyethylene glycol 400, pH 10-11), 3, 10 and 30 mg/kg/day of lansoprazole. The volumes of administration were 5, 1.67 and 0.5 ml/kg in 30, 10 and 3 mg/kg groups respectively. The rate of administration was 1 ml/min. The control group rats were given saline or vehicle (5 ml/kg) in similar fashion. The male rats were treated from 9 weeks prior to mating, throughout mating period and until they were sacrificed. Females were treated from 2 weeks before mating, throughout mating period and up to day 7 of gestation. All rats were observed twice daily for clinical signs and mortality. Body weights were recorded on days 0, 6, 13, 18 and 20 of gestation. Food intakes were recorded on days 0, 6, 8, 13, 17 and 19 of gestation. All dams were sacrificed on day 20 of gestation and were examined for the number of corpora lutea, the number of implants, the number of dead or resorbed fetuses and number of live fetuses. All fetuses were examined for gross external anomalies. About two-third of the fetuses from each litter were examined for skeletal major/minor abnormalities and the remaining one-third fetuses were examined for visceral abnormalities and variations.

Results: In high dose treated males, body weight gains were reduced by 7% when compared to control values. Treatment had no significant effect on body weight gains in females. In both sexes, treatment had no significant effect on food intakes. No treatment related effects were seen on number of corpora lutea, number of implants, number of live fetuses, sex ratio and weight of the fetuses. No treatment related abnormalities were observed in fetuses, upon external, visceral and skeletal examinations.

Dams Sacrificed on Day 20 of Gestation					
Parameters	Control	Vehicle	Low Dose	Mid Dose	High Dose
# of female mated	21	22	22	22	22
# of pregnant females	21	19	22	19	21
Pregnancy rate (%)	100.0	86.4	100.0	86.4	95.5
3 of corpora lutea/dam	15.6 ± 1.2	15.8 ± 1.8	16.0 ± 1.5	15.6 ± 1.3	15.7 ± 1.2
# of implants/dam	13.8 ± 2.7	14.7 ± 1.5	14.5 ± 3.6	14.3 ± 3.4	14.1 ± 2.9
Pre-implantation loss (%)	11.8	6.6	9.3	9.0	10.1
Post-implantation loss (%)	5.2	5.8	6.9	3.5	4.3
Live fetuses/dam	13.0 ± 2.7	13.9 ± 1.8	13.4 ± 3.3	13.7 ± 3.4	13.5 ± 2.9
Sex ratio (% males)	54.4	56.7	51.3	55.3	52.6
Mean fetal weight (g)					
Males	3.07 ± 0.25	2.94 ± 0.20	2.92 ± 0.21	2.80 ± 0.38	2.94 ± 0.21
Females	2.84 ± 0.18	2.77 ± 0.14	2.73 ± 0.19	2.58 ± 0.35	2.79 ± 0.18

In this study, there were no effects on the fertility and mating performance of the treated male and female rats at i.v. doses up to and including 30 mg/kg/day of lansoprazole.

Embryofetal development

Study title: Segment II. I.v. teratology study in rats

Key study findings: Pregnant rats were given lansoprazole intravenously at 0, 10, and 30 mg/kg/day during gestation days 6- 17. The results indicated that treatment with lansoprazole did not produce any embryotoxicity and teratogenic effects at doses up to 30 mg/kg/day.

Study no.: A-29-1783

Volume # 1.15, and page #: 001

Testing Laboratories: [

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Dates Study Started and Completed: Not given

Report Date: December 25, 1992

GLP Requirements: Not mentioned

Test Species: Pregnant Jcl: Wistar rats

No. of Animals: 13-14 pregnant rats/group

Drug Batch No.: Z 338201 (each vial contained 30 mg of AG-1749, 3.7 mg of NaOH, 10 mg of malumine and 60 mg of mannitol)

Vehicle: PEG formulation (adjusted to pH 10-11 with 0.1 NaOH)

Methods: Pregnant rats were given I.V. doses of 0 (saline), 0 (vehicle: "PEG Formulation"), 10 and 30 mg/kg of Lansoprazole from day 6 to 17 of gestation. The volume of administration was 10 ml/kg and rate of administration was 1.5-2 ml/min. All dams were observed daily. Body weight and food consumptions were recorded on days 0, 6, 8, 10, 13, 15, 18 and 20 of gestation. On day 20 of gestation all dams were sacrificed and examined for number of corpora lutea, the number of implants, the number of dead or resorbed fetuses and number of live fetuses. Live fetuses were weighed, sexed and examined for external abnormalities. Approximately one-third of the fetuses were examined for visceral abnormalities and the remaining two-third fetuses were examined for skeletal malformations and variations.

Results: A total of 3 dams (1 from vehicle control group and 2 from high dose group) died during the study period due to respiratory failure. These deaths were not considered to be treatment related. No treatment related findings were evident in dams except thymus weights were decreased by 40% in high dose treated dams compared to vehicle control values. There were no significant changes in pregnancy parameters (mean number of corpora lutea, number of implants, pre- and post-implantation loss, number of live/dead fetuses and weight of the fetuses). No treatment related abnormalities were observed on external, skeletal and visceral examinations in any group. Thus the highest test dose (30 mg/kg/day) was maternal toxic. However, no embryotoxic and teratogenic effects at dosage up to 30 mg/kg/day was observed.

Study title: Segment II. I.v. teratology study in rats

Key study findings: Pregnant rats were given lansoprazole intravenously at 0, 3, 10, and 30 mg/kg/day during gestation days 6- 17. The results indicated that treatment with

lansoprazole did not produce any embryotoxicity and teratogenic effects at doses up to 30 mg/kg/day.

Study no.: A-29-2065

Volume # 1.16, and page #: 001

Testing Laboratories: [

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Study Started: April 26, 1993

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Study Completed: September 8, 1994 (report date).

GLP Requirements: A Statement of Compliance with GLP regulations was included.

Animals: Pregnant Jcl:Wistar rats.

Drug Batch No.: Z338704.

Methods: Sponsor has earlier submitted the results of i.v. Segment II teratology study in rats (report # A-29-1783: 0, 10 and 30 mg/kg/day) in which no teratogenic effects were seen at doses up to 30 mg/kg/day (for detail see review dated September 6, 1993). Pregnant rats (34-36/group) were given i.v. doses of 0 (saline), 0 (vehicle: polyethylene glycol 400, pH 10-11), 3, 10 and 30 mg/kg/day of lansoprazole from day 6 to 17 of gestation. The volumes of administration were 5, 1.67 and 0.5 ml/kg in 30, 10 and 3 mg/kg groups respectively. The rate of administration was 1 ml/min. The control group rats were given saline or vehicle (5 ml/kg) in similar fashion. All dams were observed twice daily for clinical signs and mortality. Body weights were recorded on days 0, 6, 8, 10, 13, 15, 18 and 20 of gestation and on days 0, 4, 7, 14 and 22 of lactation. Food intakes were recorded on days 0, 6, 8, 10, 13, 15 and 18 of gestation. About two-thirds dams were sacrificed on day 20 of gestation and examined for the number of corpora lutea, the number of implants, the number of dead or resorbed fetuses and number of live fetuses. The live fetuses were weighed and sexed. Approximately two-thirds of fetuses eviscerated and examined for skeletal major/minor abnormalities, the remaining fetuses were examined for visceral abnormalities and variations. The remaining dams were allowed to deliver spontaneously. On day 4 of lactation culling was carried out to achieve 4 males and 4 females (if possible) per litter. The offspring were reared by the dams until day 22 of post-partum. During the nursing period the growth and differential of the pups were observed and development parameters were assessed. One male and one female of the F₁ generation from the same group were continuously mated. All F₁ dams were allowed to deliver. All F₁ dams and F₂ pups were killed on day 7 of lactation and examined as mentioned above.

Results:

Dams Sacrificed at Day 22: One dam in high dose group died on day 10 of gestation. The cause of death could not be established. During the treatment period body weight gains were decreased by 9.2% in high dose treated dams. Food intakes in high dose treated dams were decreased by 11% during gestation days 6 through 13. The number of corpora lutea, number of

implants, pre-implantation loss, post-implantation loss, number of live/dead fetuses, fetal weights and sex ratio were comparable in all groups. No treatment related abnormalities were observed on external, skeletal and visceral examination in any groups.

Effects of Lansoprazole on Maternal and Fetal Parameters in Rats					
Parameters	Saline Control	Vehicle Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
# of pregnant	23	23	22	23	22
# of corpora lutea/dam	16.7 ± 3.0	15.5 ± 2.0	15.9 ± 1.5	15.9 ± 1.3	15.8 ± 1.3
# of implants/dam	14.6 ± 2.9	14.7 ± 2.5	14.9 ± 1.5	15.0 ± 1.2	14.5 ± 1.0
Pre-implantation loss (%)	9.8 ± 18.2	5.9 ± 10.7	6.2 ± 5.9	5.0 ± 6.1	7.6 ± 8.0
Post-implantation loss (%)	9.1 ± 16.6	7.7 ± 9.4	7.4 ± 8.9	8.6 ± 6.7	5.5 ± 5.3
Mean live fetuses/dam	13.6 ± 3.6	13.6 ± 2.8	13.8 ± 2.1	13.8 ± 1.8	13.8 ± 1.3
# of dead fetuses/dam	0.0 ± 0.2	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3
Mean Fetal Wt. (g):					
Males	2.96 ± 0.22	2.99 ± 0.13	2.96 ± 0.20	2.97 ± 0.14	2.81 ± 0.18
Females	2.73 ± 0.31	2.81 ± 0.21	2.83 ± 0.22	2.79 ± 0.16	2.70 ± 0.19
Sex ratio (% males)	50.7	52.2	47.7	51.3	50.5
# of fetuses (litters) Examined for External malformation	313 (23)	312 (23)	304 (22)	317 (23)	304 (22)
# of fetuses (litters) Examined for Visceral malformation	123 (23)	120 (23)	118 (22)	120 (23)	118 (22)
# of fetuses (litters) Examined for Skeletal malformation	190 (22)	192 (23)	186 (22)	197 (23)	186 (22)
No treatment related malformation was seen in external, visceral and skeletal examinations.					

Dams Allowed to Deliver: No significant differences in the gestation period between the groups were noted. Treatment had no significant effect on delivery index (# of pup born x 100/# of implants), viability index on day 4 and 22 of lactation, post-natal development and differentiation. There was no significant effect on fertility test and mating performance test of F₁-generation rats. No drug related abnormalities were seen in F₂ pups at necropsy.

In this study, no teratogenic effect at dosages up to 30 mg/kg/day was seen in rats.

Study title: Segment II. I.v. teratology study in rabbits

Key study findings: Pregnant rabbits were given lansoprazole intravenously at 0, 10, and 30 mg/kg/day during gestation days 6-18. The results indicated that treatment with lansoprazole did not produce any embryotoxicity and teratogenic effects at doses up to 30 mg/kg/day.

Study no.: A-29-2066

Volume # 1.17, and page #: 001

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Testing Laboratories: C

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Study Started: September 14, 1993**Study Completed:** November 15, 1994**GLP Requirements:** A Statement of Compliance with GLP regulations was included.**Animals:** KBL:JW rabbits (Males: 33-93 weeks old, 3.29-4.46 kg and Females: 16-20 weeks old, 2.86-3.87 kg).**No. of Animals:** 14-15 pregnant females/group.**Drug Batch No.:** Z338704

Methods: Pregnant rabbits were given i.v. doses of 0 (saline), 0 (vehicle: polyethylene glycol 400 pH 10-11), 3, 10 and 30 mg/kg/day of lansoprazole. The volumes of administration were 5, 5, 0.5, 1.67 and 5 ml/kg for 0 (saline), 0 (vehicle), 3, 10 and 30 mg/kg/day dose groups respectively. The rate of administration was 1 ml/min. The duration of treatment was from day 6 to day 18 of gestation. All animals were observed twice daily (before and 0.5 to 2 hr post dosing). Body weights were recorded on day 0, 6, 9, 12, 15, 19, 22, 25 and 28 of gestation. Food intakes were recorded on days 0, 6, 9, 12, 15, 18, 22, 25 and 27 of gestation. All dams were sacrificed on day 28 of gestation and were examined for the number of corpora lutea, number of implants, number of live/dead fetuses. Live fetuses were weighed, sexed and examined for external, visceral and skeletal abnormalities.

Results: Four dams (1 each from vehicle control and low dose groups and 2 from high dose group) aborted their litters on days 19-24 of gestation. These abortions were considered not to be treatment related. There was an indication of decreased body weight gains and food intakes in high dose treated dams. The number of corpora lutea, the number of implants, pre-implantation loss, post-implantation loss, sex ratio, and fetal weights were comparable in all groups. No treatment related abnormalities were seen in external, skeletal and visceral examinations in any groups.

Effects of Lansoprazole on Maternal and Fetal Parameters in Rabbits					
Parameters	Saline Control	Vehicle Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
# of Pregnant	14	14	13	14	13
# of Corpora Lutea/dam	10.5 ± 2.1	9.1 ± 2.1	10.3 ± 2.2	10.0 ± 2.0	8.5 ± 2.0
# of Implants	8.4 ± 2.7	8.1 ± 2.4	9.4 ± 2.1	8.5 ± 2.6	6.5 ± 3.5
Pre-implantation Loss (%)	19.4 ± 22.7	12.0 ± 11.0	8.9 ± 8.0	14.5 ± 19.8	27.6 ± 33.2
Post-implantation Loss (%)	2.7 ± 8.2	7.0 ± 12.2	5.7 ± 9.9	4.6 ± 7.9	2.4 ± 4.6
Mean Live Fetuses/dam	8.1 ± 2.6	7.6 ± 2.5	8.8 ± 1.9	8.1 ± 2.5	6.3 ± 3.3
Sex Ratio (% male)	43.4	51.5	51.4	40.9	48.5
Mean Fetal Wt. (g):					
Males	39.6 ± 4.7	38.0 ± 3.7	38.6 ± 4.0	37.5 ± 4.2	40.5 ± 7.0
Females	39.7 ± 4.4	37.7 ± 4.4	38.7 ± 5.4	36.9 ± 4.9	40.2 ± 6.0
# of Fetuses (litters) Examined for External malformation	113 (14)	106 (14)	114 (13)	113 (14)	82 (13)
# of fetuses (litters) Examined for Visceral malformation	113 (14)	106 (14)	114 (13)	113 (14)	82 (13)
# of fetuses (litters) Examined for skeletal malformation	113 (14)	106 (14)	114 (13)	113 (14)	82 (13)
No treatment related malformation was seen in external, visceral and skeletal examinations.					

In this study, no teratogenic effects at doses up to 30 mg/kg/day was seen in the rabbits.

Prenatal and postnatal development

Study title: I.v. Segment III perinatal and postnatal study in rats

Key study findings: Pregnant rats were given lansoprazole intravenously at 0, 10, and 30 mg/kg/day from gestation days 15 to day 21 of lactation. The results indicated that treatment with lansoprazole did not produce any adverse effects at doses up to 30 mg/kg/day in this study.

Study no.: A-29-2067

Volume # 1.17, and **page #:** 001

Testing Laboratories: [

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Study Started: June 2, 1993

Study Completed: November 8, 1994

GLP Requirements: A Statement of Compliance with GLP regulations was included.

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Test Species: Pregnant Jcl:Wistar rats (males: 12 weeks old, 375-414 g, and females: 12-16 weeks old, 202-275 g).

No. of Animals: 22-23/group.

Route of Administration: I.V.

Drug Batch No.: Z338704

Methods: Pregnant rats were given i.v. doses of 0 (saline), 0 (vehicle: polyethylene glycol 400, pH 10-11), 3, 10 and 30 mg/kg/day of lansoprazole from day 15 of gestation to day 21 of lactation. The volumes of administration were 5, 5, 0.1, 1.67 and 5 ml/kg for C (saline), 0 (vehicle), 3, 10 and 30 mg/kg/day dose groups respectively. The rate of administration was 1 ml/min. All dams were observed twice daily for clinical signs. Body weights were recorded on days 0, 6, 13, 15, 17, 20 of gestation and on days 0, 4, 7, 14 and 22 of lactation. All dams were allowed to deliver spontaneously and raise their offspring. The number of live/dead pups were recorded, and the live pups were weighed and sexed. On day 22 of post-partum all dams were sacrificed and necropsied. Pups were also weighed on days 4, 7, 14 and 22 of post-partum. On day 4 of post-partum, culling was carried out to make 8 pups (4 male and 4 female) per litter. During nursing period the growth and differentiation of the pups were observed and development parameters were assessed. At 12 weeks of age, one male and one female of the F₁ generation from the same group were continuously mated and allowed to deliver spontaneously. F₁ dams and F₂ pups were killed on day 7 of lactation and examined for any abnormalities.

Results: One dam in the vehicle control group, one in the 3 mg/kg group and one in the 30 mg/kg group died immediately after dosing on day 18 of lactation, day 15 of gestation and day 6 of lactation respectively. Cause of death could not be established. In high dose treated dams body weight gains during gestation period (day 6-20) were decreased by 10.8% when compared to the vehicle control values. During lactation period body weight gains were reduced by 43%, 50% and 43% in low, mid and high dose groups respectively when compared to vehicle control values (respective decreases in body weight gains were 23%, 32% and 23% when compared to saline control group values). Food intakes were not affected by the treatment. In high dose treated dams, significant decrease (34-40%) in thymus weight was seen, when compared to either control (saline or vehicle) values. Treatment had no significant affect on duration of gestation, viability indexes at birth, on day 4 and day 22 of lactation. Body weights of F₁ pups were comparable in all groups. No drug related effects were seen in F₁ pups during postnatal period.

Development of F₁ pups were comparable in all groups. No treatment related effects were seen in external, visceral or skeletal examinations in F₁ pups. There was no significant effect on fertility test and mating performance test of F₁-generation rats, and no abnormalities were seen in F₂ pups.

Segment III Perinatal and Postnatal Study in Rats					
Parameters	Saline Control	Vehicle Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Total Mated	23	25	23	23	23
# of Pregnant	22	22	22	23	23
% Pregnant	95.6	88.0	95.6	100.0	100.0
# of Pregnant Evaluated	22	22	21	23	23
Length of Gestation (days)	21.5	21.7	21.6	21.6	21.6
# of Implants/dam	15.1 ± 1.6	15.2 ± 1.7	15.0 ± 2.9	15.2 ± 1.5	15.3 ± 1.4
# of Live Pups/dam on Day 1	14.0 ± 1.7	14.4 ± 2.0	13.6 ± 3.4	14.3 ± 1.4	14.0 ± 1.3
Sex Ratio (% male)	53.9	50.0	48.4	51.8	52.5
Viability Index at Day 0	93.2	92.6	86.6	92.6	94.3
Viability Index at Day 4	78.7	89.4	79.7	89.1	90.3
Viability Index at Day 22	90.1	98.1	100.0	99.4	99.4

In this study, no adverse effects were seen in rats following i.v. administration of up to 30 mg/kg/day of lansoprazole during perinatal and post natal period in rats.

3.4.7 Local Tolerance

Study title: I.v. irritation study in rabbits

Study no.: A-29-900 and A-29-1780

Volume # 1.14, and page #: 001

Methods: Male Japanese White rabbits (n=6/group) was given a single injection of saline, Lansoprazole (9 mg or 18 mg dissolved in 1 ml PEG) or positive control (sulfobromophthalein sodium [BSP] into ear vein. The volume of administration was 3 ml and given at the rate of 1 ml/min. One, 2, 3, 5, 7, 10 and 14 days after treatment, injection sites were examined for local irritation, thrombus formation, erythema and swelling of the auricle. Two and 14 days after the injection 3 rabbits/group were sacrificed and injection sites were examined microscopically.

Results: Slight edema and inflammatory cell infiltration but no thrombus were seen in Lansoprazole treated rabbits up to 2 days after injection. These changes disappeared within 14 days after drug administration. No abnormalities were seen in saline

treated rabbits and the positive control treated rabbits showed expected results. Similar results were seen when 3 or 6 mg/ml of AG-1749 were used (report # A-29-1228) in the above experiment. Thus slight i.v. irritation was seen by AG-1749 i.v. formulation.

Study title: Paravenous irritation study in rabbits

Study no.: A-29-1818

Volume # 1.14, and page #: 001

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Methods: Male Japanese White rabbits (n=6/group) a single s.c. injection of saline, Lansoprazole (0.75 or 3 mg/ml) or Omeprazole (4 mg/ml) near the posterior ear vein. The volume of injection was fixed at 0.3 ml/site. One, 2, 3, 5, 7, 10 and 14 days after treatment, injection sites were examined for local irritation, thrombus formation, erythema and dilation of the veins and venules. Two and 14 days after injection, 3 rabbits/group were sacrificed and injection sites were examined microscopically.

Results: Only Lansoprazole (0.3 ml of 3 mg/ml) and Omeprazole (0.3 of 4 mg/ml) produced edema, "interstitial cell" proliferation, inflammatory cell infiltration and hemorrhage (only in Lansoprazole group) at the injection sites, and this effect lasted for only 2 days. The severity of these effects were greater in Lansoprazole treated rabbits than Omeprazole treated rabbits. However, these changes disappeared within 14 days after drug administration. No abnormalities were seen in saline treated rabbits. Similar results were seen when 3 or 6 mg/ml of AG-1749 were used (report # A-29-1228) in the above experiment.

Study title: Intravenous irritation study of formulated AG-1749 for injection, dissolved in saline, rabbits

Study no.: A-29-2718
Volume # 1.14, and **page #:** 001

Methods: Three ml AG-1749 in saline at 6 mg/ml was injected once into the vena auricularis posterior of male rabbits (six rabbits). All animals were observed for clinical signs of toxicity. Injection sites were examined histopathologically.

Results: There were no treatment related clinical signs of toxicity. Mild adema and minimal inflammatory cell infiltration were observed 2 days after the injection. These changes were not seen on day 14 after the injection.

Study title: Intravenous Tolerance study of AG-1749 for injection, dissolved in distilled water in rabbits

Study no.: A-29-02995
Volume # 1.14, and **page #:** 001

Methods: To compare the intravenous irritation of AG-1749 in distilled water or saline at 6 mg/ml, 3 ml AG-1749 in distilled water or saline at 6 mg/ml was also injected once into the vena auricularis posterior of male rabbits (six rabbits/group).

Clinical signs of toxicity and body weight were determined. Injection sites were examined histopathologically.

Results: There were no treatment related clinical signs of toxicity and body weight. Slight adema and slight inflammatory cell infiltration were observed in the distilled water group 2 days after the injection. Slight or moderate adema and slight or moderate inflammatory cell infiltration were also observed in the saline group 2 days after the injection. In addition, slight thrombus was noted at one site. These changes were not seen on day 14 after the injection. The results suggested that the intravenous tolerability of AG-1749 dissolved in distilled water is similar to that dissolved in saline.

3.4.8 Special toxicology studies

Study title: In vitro hemolysis of formulated AG-1749 for injection, Dissolved in Saline, using Rabbit blood

Study no: A-29-2717
Volume #: 1.14, and **page #:** 001

Methods: Rabbit blood (0.5 ml) was mixed with 0.05 or 0.5 ml of the AG-1749 solution (6 mg/ml). The mixture was incubated at 37° C for 1 minute and then centrifuged at 18,600 g for 1 minute. The supernatant was examined macroscopically.

Results: No hemolysis was observed.

Study title: Hemolytic potential of lansoprazole in rats

Study no.: A-29-902 and A-29-1782
Volume # 1.14, and **page #:** 001

Methods: In study A-29-902 five male Wistar rats were given saline or 0.5 mg/kg/ of Lansoprazole (dissolved in polyethylene glycol, final concentration 3 mg/ml, pH 10-11) intravenously via tail vein as a 30 second bolus. In study A-29-1782, the above study was repeated and rats were injected with 1 mg/kg of Lansoprazole (6 mg/ml, pH 10-11). Thirty minutes after the injection, blood samples were collected from abdominal aorta. Percent neurolysis was determined spectrometrically.

Results: No hemolysis was evident.

Study title: Hemolytic potential of lansoprazole in rabbits

Study no.: A-29-901 and A-29-1781

Volume # 1.14, and page #: 001

Methods: Rabbit blood (0.1 ml) was added to 1 ml incubation mixture containing 0, 1.4, 3 or 6 mg of Lansoprazole (solvent for Lansoprazole was PEG) and incubated at 37°C for 5 or 30 minutes. At the end of incubation period percent hemolysis was monitored spectrometrically.

Results: No hemolysis was evident, except at 30 minutes time point 5% and 20% hemolysis were seen in systems containing 3 and 6 mg/ml of Lansoprazole respectively.

Study title: In vitro hemolysis of formulated AG-1749 for injection, Dissolved in distilled water, using Rabbit blood

Study no: A-29-02992

Volume #: 1.14, and page #: 001

Methods: Rabbit blood (0.5 ml) was mixed with 0.05 or 0.5 ml of the AG-1749 solution (6 mg/ml). The mixture was incubated at 37° C for 1 minute and then centrifuged at 18,600 g for 1 minute. The supernatant was examined macroscopically.

Results: No hemolysis was observed.

LABELING:

The labeling is according to 21 CFR, Subpart B. The following revisions in the labeling are recommended.

1. Sponsor's Version:

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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Evaluation: The i.v dose of 30 mg/kg/day in rats is about 8 times the recommended human dose based on body surface area.

Suggested Version:

Lansoprazole at intravenous doses up to 30 mg/kg/day (approximately 8 times the recommended human dose of 30 mg daily, based on body surface area) was found to have no effect on fertility and reproductive performance in male and female rats.

2. Sponsor's Version:

PREGNANCY

Pregnancy Category B

[]
However, there are no adequate and well-controlled studies in pregnant women using the intravenous route. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Evaluation: The i.v. dose of 30 mg/kg/day in rats and rabbits is about 8 and 16 times the recommended human dose, respectively, based on body surface area.

Suggested Version:

Teratology studies have been conducted in rats and rabbits using intravenous doses of up to 30 mg/kg/day (approximately 8 times in rats or 16 times in rabbits of the recommended human dose based on body surface area). Lansoprazole did not result in any impairment of fertility or harm to the fetus.

However, there are no adequate and well-controlled studies in pregnant women using the intravenous route. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

3. Sponsor's version:

OVERDOSE

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Evaluation: Adequate findings from the acute i.v. toxicity studies were not included. The second paragraph of the OVERDOSE is not related to the clinical intravenous formulation and should be removed.

Suggested Version:

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Lansoprazole is a substituted benzimidazole and belongs to a class of antisecretory compounds. It suppresses gastric acid secretion by specific inhibition of the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell and blocks the final step of acid production. It was demonstrated that intravenous administration of lansoprazole inhibited basal gastric acid secretion at ID₅₀ of 1.67 mg/kg in rats and histamine-induced gastric acid secretion at ID₅₀ of 0.28 mg/kg in rats and 0.14 mg/kg in dogs. Inhibition of gastric acid secretion was also demonstrated following intravenous administration of lansoprazole at 30 mg/kg in humans. The suppression of acid secretion following intravenous administration was as or more effective than oral administration of lansoprazole.

In the present NDA, sponsor is seeking for approval to market prevacid intravenous infusion for the short term treatment (up to 7 days) of all grades of erosive esophagitis when patients are unable to take the oral formulation. In support of this NDA, following preclinical studies were submitted in this NDA: single i.v. dose toxicity studies in mice, rats, and dogs, 1-week, 2-week, 4-week, and 13-week i.v. toxicity studies in rats and dogs, i.v. Segment I fertility and reproductive performance toxicity studies in rats, i.v. Segment II teratologic studies in rats and rabbits, i.v. Segment III peri- and post-natal reproductive toxicity study in rats, and special toxicity studies.

The pharmacokinetic studies indicated that following intravenous administration of lansoprazole the plasma level of the unchanged drug declined quickly with t_{1/2} of 0.3 hours in rats, and t_{1/2α} of 0.6 hours and t_{1/2β} of 0.6-11 hours in dogs. In humans, the plasma level of lansoprazole decreased rapidly with

$t_{1/2}$ of ~1 hour following both oral and i.v. administrations. The metabolic patterns of lansoprazole were similar following oral and i.v. administrations in rats and dogs. Irrespective of the route of administration (oral or i.v.), approximately 26-32% and 64-69% radioactivity were excreted in the urine and feces, respectively, over 72 hours in both rats and dogs. Intravenous administration of lansoprazole produces higher systemic exposure as compared to the oral administration in both animals and humans.

The acute i.v. toxicity studies were conducted in mice and rats with AG-1749 in Saline. The minimal lethal dose was 218 mg/kg in male mice and 167 mg/kg for female rats. The deaths occurred immediately after the injection. The minimal lethal dose for female mice and male rats were not identified. The non-lethal dose in mice was 167 mg/kg for males and 218 mg/kg for females. The non-lethal dose in rats was 167 mg/kg for males and 128 mg/kg for females. Following clinical signs of toxicity were noted in both mice and rats: decrease in locomotor activity, decreased respiration, depression of touch-escape response, flattened posture or lying on side, ataxia gait. In addition, tonic convulsion and decreased body temperature in mice and ptosis in rats were noted.

The results of the acute i.v. toxicity studies with AG-1749 in polyethylene glycol 400 indicated that AG-1749 in polyethylene glycol 400 was more lethal than AG-1749 in saline. However, the clinical signs of toxicity observed in the acute i.v. toxicity studies with AG-1749 in polyethylene glycol 400 were similar to those seen with AG-1749 in saline. Since polyethylene glycol 400 is not used in clinical formulation, the results of the acute i.v. toxicity studies with AG-1749 in polyethylene glycol 400 are not relevant to the drug product of prevacid i.v. injection.

In the 2-week i.v. toxicity study in rats, lansoprazole was given to rats intravenously at 0, 1, 3, and 10 mg/kg/day for 2 weeks. The high dose of 10 mg/kg/day was no effect dose.

In the 4-week i.v. toxicity study in rats, lansoprazole was given to rats intravenously at 0, 3, 10, and 30 mg/kg/day for 4 weeks. The high dose of 30 mg/kg/day was no effect dose.

In another 4-week i.v. toxicity study in rats, AG-1749 was given intravenously to male rats at 0 and 60 mg/kg/day for 4 week. The results indicated that one treated animal was found dead and another treated animal was sacrificed due to severe

damage at the injection sites. The study was terminated on day 26 due to severe lesions at the injection site. Following toxicity were observed in the treated animals: bradypnea, hypoactivity, decreased body weight gain and food consumption, and inflammation at the injection sites.

In the 13-week i.v. toxicity study in rats, lansoprazole was given to rats intravenously at 0, 3, 10, 30, and 60 mg/kg/day for 13 weeks. Histopathological examination revealed eosinophilic chief cells, hypertrophy and hyperplasia of the chief cells and microaggregation of the ECL cells in the stomach, atrophy of the thymus, and hypertrophy of the centrilobular hepatocytes in all treatment groups, suggesting that the stomach, thymus, and liver were the target organs of toxicity. No effect dose was not identified. Lansoprazole was tolerated at dose of 10 mg/kg/day.

In the 2-week i.v. toxicity study in dogs, lansoprazole was given to dogs intravenously at 0, 1, 3, and 10 mg/kg/day for 2 weeks. The high dose of 10 mg/kg/day was no effect dose.

In the 4-week i.v. toxicity study in dogs, lansoprazole was given to dogs intravenously at 0, 3, 10, and 30 mg/kg/day for 4 weeks. The histopathological examination revealed that hypertrophy and single cell necrosis of parietal cells in the stomach, suggesting that the stomach was the target organs of toxicity. The dose of 3 mg/kg/day was no effect dose.

In the 13-week i.v. toxicity study in dogs, lansoprazole was given to dogs intravenously at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Histopathological examination revealed inflammation and fibrosis of the vein wall and perivenous tissues in all treatment groups and the severity was dose related. Hyperplasia of the glandular neck and foveolar region of the fundic glands and atrophy of the parietal cells of the stomach were found in the treated dogs.

In the repeated 13-week i.v. toxicity study in dogs, Lansoprazole was given to dogs intravenously at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Histopathological examination revealed atrophy, vacuolation and necrosis of the parietal cells, and hyperplasia of the foveolar and neck region of the stomach in all treated dogs. These alterations were more severe in the high dose group.

In the i.v. Segment I. Fertility and general reproductive performance study in male rats, male rats were given

lansoprazole intravenously at 0, 3, 10, and 30 mg/kg/day for 9 weeks before mating and throughout the mating phase and until they were sacrificed. The results indicated that treatment with lansoprazole did not affect fertility and mating performance of the male rats at intravenous doses up to 30 mg/kg/day. The dose selection was adequate and the dose 30 mg/kg/day was the maximum tolerated dose.

In the i.v. Segment I. Fertility and general reproductive performance study in rats, rats (males and females) were given lansoprazole intravenously at 0, 3, 10, and 30 mg/kg/day. Males were treated for 9 weeks before mating and throughout the mating phase and until they were sacrificed. Females were treated for 2 weeks before mating, throughout mating, and until day 7 of gestation. The results indicated that treatment with lansoprazole did not affect fertility and mating performance of the male and females rats at intravenous doses up to 30 mg/kg/day. The dose selection was adequate.

In the i.v. Segment II. teratology study in rats, pregnant rats were given lansoprazole intravenously at 0, 10, and 30 mg/kg/day during gestation days 6-17. The results indicated that treatment with lansoprazole did not produce any embryotoxicity and teratogenic effects at doses up to 30 mg/kg/day. The dose selection was adequate.

In the i.v. Segment II. teratology study in rats, pregnant rats were given lansoprazole intravenously at 0, 3, 10, and 30 mg/kg/day during gestation days 6-17. The results indicated that treatment with lansoprazole did not produce any embryotoxicity and teratogenic effects at doses up to 30 mg/kg/day. The dose selection was adequate.

In the i.v. Segment II. teratology study in rabbits, pregnant rabbits were given lansoprazole intravenously at 0, 10, and 30 mg/kg/day during gestation days 6-18. The results indicated that treatment with lansoprazole did not produce any embryotoxicity and teratogenic effects at doses up to 30 mg/kg/day. The dose selection was adequate.

In the i.v. Segment III perinatal and postnatal study in rats, pregnant rats were given lansoprazole intravenously at 0, 10, and 30 mg/kg/day from gestation days 15 to day 21 of lactation. The results indicated that treatment with lansoprazole did not produce any adverse effects at doses up to 30 mg/kg/day in this study. The dose selection was adequate.

In vitro hemolytic studies revealed no hemolytic potential in rabbit blood at lansoprazole concentration of 6 mg/ml (1:1 mixture). Intravenous injection of lansoprazole (6 mg/ml) produced mild edema and inflammatory cell infiltration at the injection site in rabbits.

Lansoprazole was not genotoxic in the Ames test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, the in vivo mouse micronucleus test or the rat bone marrow cell chromosomal aberration test. It was positive in in vitro human lymphocyte chromosomal aberration assays.

In a 24-month oral carcinogenicity study, lansoprazole at doses of 15 to 600 mg/kg/day produced a dose-related increased incidence of gastric ECL cell hyperplasia in CD-1 mice. It also increased the incidence of liver tumors (hepatocellular adenoma plus carcinoma) and the incidence of adenoma of rete testis.

In two 24-month oral carcinogenicity studies, lansoprazole at doses of 5 to 150 mg/kg/day produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes and the incidence of testicular interstitial cell adenomas in male rats.

In rats, the stomach, thymus (atrophy of the thymus), and liver (hypertrophy of the centrilobular hepatocytes) were identified as target organs of toxicity. Histopathological examination revealed eosinophilic chief cells, hypertrophy and hyperplasia of the chief cells and microaggregation of the ECL cells in the stomach.

In dogs, the stomach was the target organ of toxicity. Histopathological examination revealed atrophy, vacuolation and necrosis of the parietal cells, and hyperplasia of the foveolar and neck region of the stomach.

The systemic exposure following intravenous administration of 30 mg/kg/day in rats (13-week i.v. toxicity study in rats) was approximately 2.6-3 times that following the recommended human intravenous dose of 30 mg based on plasma AUC values.

The systemic exposure following intravenous administration of 30 mg/kg/day in dogs (13-week i.v. toxicity study in dogs) was approximately 11 times that following the recommended human intravenous dose of 30 mg based on plasma AUC values.

CC:

NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Choudary

HFD-180/Dr. Zhang

HFD-048/Dr. Viswanathan

R/D Init.: J. Choudary 8/29/03

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/s/

Ke Zhang
9/8/03 09:09:11 AM
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Jasti Choudary
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Necessary changes for the labeling have been incorporated in
the draft labeling.