The sponsor indicated that adenocarcinomas in the female mammary glands were a random event and unrelated to treatment based on the aforementioned points. In addition, similar finding was not found in mice. However, the adenocarcinoma finding was dose-related, and if the doses were higher, a higher incidence of adenocarcinomas might have occurred.

Executive CAC Recommendations and Conclusions:

* Epinastine is a genotoxic compound. Based on available information, the high doses selected for these two studies are not adequate based on any generally accepted dose selection endpoints.
* The Committee feels that in this study, the dose-related increase in mammary adenocarcinomas in female rats is not a clear indication of a positive finding, however, it can not be dismissed given the inadequacy of the dose selection.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC
cc:\
cc:\
/Division File, HFD-550
/ZChen, HFD-550
/ROsterberg, HFD-550
/RRodriguez, HFD-550
/ASeifried, HFD-024

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/s/

Joseph DeGeorge
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Recommended labeling:

In 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses up to 40 mg/kg [approximately 30,000 times higher than the maximum recommended ocular human dose (MROHD) of 0.0014 mg/kg/day on a mg/kg basis, assuming 100% absorption in humans and animals].

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Studies reviewed:

U87-0466: Fertility and general reproduction study with the substance WAL 801 CL in male and female rats (Segment I). Vol. 24, Page 001
U82-0063: Teratogenicity of WAL 801 CL in rats. Vol. 20, Page 209
U84-0243: Teratogenicity of WAL 801 CL in rabbits. Vol. 20, Page 312
U87-0806: Perinatal and postnatal study (Segment III) in rats (oral administration). Vol. 24, Page 337
U96-0244: Single dose toxicity study of WAL 801 CL in new-born rats by oral administration. Vol. 36, Page 082

U87-0466: Fertility and general reproduction study with the substance WAL 801 CL in male and female rats (Segment I). Vol. 24, Page 001

Key study findings: Maternal toxicity including decreased body weight gain and food consumption was noted at the high dose (120 mg/kg). Mating index was similar in all groups. However, the fertility index (pregnant rate) was decreased in HD animals, which might be related to the slight irregularities of the estrous cycles. The reduced conception rate was not due to male infertility. In HD group, fetal body weight, pup body weight, and pup body weight gain during lactation day 1 to day 21 were decreased. A slight retardation in erection of the pinnae, fur growth, and opening of the eyes was noted in HD pups. Dosing at 120 mg/kg did not impair rats' ability to litter and rear their pups. The fertility of F_1 animals was not affected. There was no drug-related embryotoxicity or teratogenicity. The NOAEL for fertility and general reproductive performance in this study was 120 mg/kg for males and 30 mg/kg for females. The NOAEL for maternal toxicity was 30 mg/kg.

Document #: U87-0466
Study No: C45
Conducting laboratory and location: Reproduction Section, Department of Experimental Pathology and Toxicology, Boehringer Ingelheim KG, D-6507 Ingelheim am Rhein, Germany
Date of study initiation: August 1986
GLP compliance: Yes
QAU: Yes
Animal: Rats/Chbb:THOM (SPF), ♂: 7 weeks old, 152.2 g, ♀: 10 weeks old, 174.8 g, 24/group
Route: Oral (gavage)
Drug: WAL 801 (Batch #: X) in distilled water
Study design:

Group		Dose (mg/kg)	N/sex (main study)	Dose volume (ml/kg)
1	Control	Vehicle	24	5
2	Low dose	6	24	5
3	mid dose	30	24	5
4	High dose	120	24	5

The purpose of this study was to determine the potential toxic effects of WAL 801 CL on fertility and general reproductive capacity in male and female rats. The drug was given orally (by gavage) to males for 10 weeks and to females for 2 weeks prior to the start of mating, during the 3-week gestation period, and during the 3-week lactation period.

Female rats were mated with males in the ratio of 1 male: 1 female, and the day positive mating observed (a vaginal plug or sperm was detected) was designated as gestation day 1. On gestation day 22, terminal cesarean section was performed. Toxicity was assessed as shown below.

Dams:
Mortality and clinical observations: Daily
Body weights: Weekly during the 10-week (males) or 2-week (females) pre-mating phase, and daily during the pregnancy and lactation phases.
Food consumption: Weekly

Postmortem examination: Males were sacrificed after mating and were necropsied. On pregnancy day 22, half of the females were sacrificed, hysterectomized and necropsied. The other half of the dams were allowed to deliver their pups naturally and rear the pups until lactation day 21.

Reproductive parameters and fetuses:
Opening the uterus: The numbers of corpora lutea, living fetuses, dead fetuses, and early and late resorptions were determined. The litter, fetal and placental weights were also determined. The fetuses were sexed. Each fetus was examined for external malformations.
Skeletal examination: Two-thirds of the live fetuses of each litter
Visceral examination: The remaining one-third of the fetuses

Rearing group:
The neonates were examined macroscopically, weighed, and sexed. On lactation day 4, the litters were culled to 4 pups/sex/litter. The following parameters were recorded:
Erection of pinnae: Days 4 and 5
The first sign of fur growth: Days 6 and 7
Running freely: Days 12 and 13
Eruption of the maxillary incisors: Days 13 and 14
Opening of the eyes: Days 15 and 16
After weaning, the litters were culled again to 2/sex/litter. The following behavioral tests were conducted: swimming test, hearing test, sight test and water maze test.
The pups (2/sex/litter) were weighed weekly and were reared until the 10^{th} week of life. They were mated within the dose groups. Mating siblings was avoided. The mated females were terminated between pregnancy days 13 and 16, and the numbers of corpora lutea, living fetuses, dead fetuses, and resorptions were determined. Necropsy was performed on all F_0 dams and F_1 pups.

Results:

Mortality and clinical observations: One MD male, 6 HD males and one HD female died prematurely. The cause of the deaths was faulty gavage resulted from the animals' attempts to resist dosing. No treatment-related clinical signs were noted.

Body weight changes: No abnormal findings were noted in LD and MD animals. In HD males, after 10-week treatment, the body weight and body weight gain were 10% and 20% lower than those in the control males, respectively. In the females dosed for 2 weeks, HD animals had less body weight gain (15.6 g, ↓24%) than in control animals (20.4 g). In the pregnant animals of cesarean-section groups, body weight and body weight gain were comparable between control and treated groups. In the naturally delivery groups, HD females showed less body weight gain (128.1 g, ↓11%) than that in the control group (143.9 g). However, the body weight of the HD animals was 94% of the control's. In the lactation phase, HD females showed less body weight gain (25.7 g, ↓20%) than that in the control group (32.0 g) but the body weight of the HD animals was 97% of the body weight in control animals.

Food consumption: No abnormal findings were noted in LD and MD animals. HD males showed less food consumption (week) than that in the control animals (

[redacted] g/week). Less food consumption was also noted in HD females during the premating period (↓9%), pregnancy period (naturally delivery animals only, 149.0 g/week vs. control's 157.8 g/week), and lactation phase (311.4 g/week vs. control's 352.3 g/week).

Estrous cycle: Slight irregularities of the 4-day rhythm (sometimes longer and sometimes shorter) were seen in 10 HD animals. However, the mating index was not affected. Prolonged estrous cycles were also seen in 2 control animals.

Mating parameters: Mating and fertility indexes are summarized in the table below. A low fertility index was noted in HD animals.

Mating and fertility indexes

Dosage (mg/kg)	Vehicle	6	30	120
Number of females used	24	24	24	24
Number of females mated	21	24	23	23
Mating index (%)	87.5	100	95.8	95.8
Number of females pregnant	21	23	23	15
Fertility index (%)	100	95.8	100	65.2

Post-mortem examinations for males: No drug abnormal findings were noted. The deaths occurred during the dosing period were due to faulty gavage. No toxicologically significant changes in testis weight were noted. Histopathological examination of the gonads of the HD animals showed no cell or tissue changes in the testicular parenchyma.

Examinations on the cesarean-section groups: No abnormal necropsy findings were noted in the animals sacrificed on pregnant day 22. Reproductive parameters are summarized in the table below. No toxicologically significant, treatment-related positive findings were noted.

Summary of maternal and fetal data at cesarean section (mean ± SD)

Dosage (mg/kg)	Vehicle	6	30	120
Females mated	10	12	11	10
Females pregnant	9	12	11	6
Maternal death	0	0	0	0
Aborted	0	0	0	0
Total resorption	0	0	0	0
Natural delivery	0	0	0	0
Pregnant at C-section	9	12	11	6
Corpora lutea/animal	13.8±1.1	13.9±2.7	15.1±1.9	14.2±1.3
Implantation/animal	13.1±1.1	12.3±3.8	14.2±2.1	13.3±1.0
Resorptions/dam	0.7±1.0	0.6±0.9	0.5±0.7	0.3±0.5
Preimplantation loss (%)	2.1±3.1	5.2±10.7	3.9±2.7	1.9±4.6
Postimplantation loss (%)	2.3±3.7	1.9±3.3	1.2±2.3	0.9±2.3
Dead fetuses	0	0	0	0
Total viable fetuses	112	141	151	78
Viable fetuses/dam	12.4±1.7	11.8±3.8	13.7±2.2	13.0±1.5
Viable male fetuses (%)	54	50	49	54
Fetal body weights. (g)	5.40±0.33	5.32±0.25	5.14±0.19	5.23±0.32
Placental weights (g)	0.45±0.04	0.45±0.10	0.44±0.04	0.45±0.08
Malformation	0	0	0	0
Variations	1 (dilatation of the right pelvis)	2/2* (hypoplasia of the 7th thoracal vetebra and dilatation of the right pelvis)	1 (short 14th rib bilateral)	0

* fetuses/litters

Examinations on the rearing groups: In the rearing groups, the mean birth weight of the neonates in HD group was slightly lower (↓3.1%) than that in the control group. The body

weight gain during lactation days 1 to 21 was also lower (↓7.4%) than control's. A slight decrease in mean pup body weights on lactation day 21 was noted in the HD group. The litter size in HD group (10.8/dam) was smaller than control group (13.2/dam). The sponsor indicated that this was because one litter only contained 2 live pups. No other toxicologically significant findings were observed.

Summary of maternal and fetal data at cesarean section (mean ± SD)

Dosage (mg/kg)	Vehicle	6	30	120
Females mated	12	12	12	12
Females pregnant	12	11	12	9
Maternal death	0	0	0	0
Aborted	0	0	0	0
Gestation period (days)	22.0±0.0	22.0±0.0	22.1±0.3	21.9±0.6
Dead pups	1	0	1	1
Total live pups on day 1	158	133	151	97
Live pups/dam on day 1	13.2±1.6	12.1±2.0	12.6±1.9	10.8±3.4
Male pups (%)	62	47	50	48
Dead pups on days 1-4	2	0	1	1
Pup loss % days 1-4	0.2±0.1	0	0.1±0.6	0.1±0.9
Dead pups on days 4-21	0	2	0	0
Pup loss % days 4-21	0	0.4±2.1	0	0
Pup body weight on day 1, (g)	6.12±0.23 (100%)	6.12±0.16 (100%)	6.02±0.18 (98.4%)	5.93±0.63 (96.9%)
Pup body weight on day 21, (g)	38.16±2.75 (100%)	40.05±2.40	38.57±2.69	35.61±5.16 (93.3%)
Body weight gain days 1-21 (g)	32.04±2.77 (100%)	33.93±2.37	32.54±2.58	29.68±4.73 (92.6%)
Malformation	0	0	1 (hydronephrosis)	0
Variations	0	0	0	0

Parameters of development and behavior of F_1 generation: Pups in the HD group showed a slight delay in erection of the pinnae, fur growth, and opening of the eyes. Necropsy examination showed hydronephrosis of right kidney in one pup. No other toxicologically significant findings were observed.

Abnormal findings in the development examination in F_1 rats

% pups		Erection of pinnae		Fur growth	Eye opening	
Dosage (mg/kg)	Litters	Day 4	Day 5	Day 7	Day 15	Day 16
Vehicle	12	7.3	91.7	100	27.1	78.1
6	11	9.2	98.9	100	29.1	84.9
30	12	5.2	87.5	100	14.6	80.2
120	9	10.6	71.2	87.9	10.6	48.5

Fertility test on the F_1 generation: The test of fertility (1 male and 1 female per litter within the same dose group, but sibling mating was avoided) was carried out. Results are summarized in the table below. There were no drug-related abnormal findings regarding fertility of the F_1 generation.

Summary of reproductive parameters of F_1 generation (mean ± SD)

Dosage (mg/kg)	Vehicle	6	30	120
Females mated	12	11	11	9
Mating index (%)	100	100	92	100
Females pregnant	11	10	11	9
Fertility index (%)	92	91	100	100
Maternal death	0	0	0	0
Aborted	0	0	0	0
Total resorption	0	0	0	0
Natural delivery	0	0	0	0
Pregnant at C-section (days 14-16)	11	10	11	9
Total corpora lutea	185	167	183	149
Total implantation	182	160	176	146
Total live fetuses	177	152	166	136
Total resorptions	5	8	10	10
Corpora lutea/animal	16.8±2.4	16.7±1.1	16.6±1.6	16.6±1.9
Implantation/animal	16.5±2.3	16.0±1.8	16.0±1.7	16.2±2.2
Live embryos/dam	16.1±2.5	15.2±2.0	15.1±1.4	15.1±2.2
Resorptions/dam	0.5±0.5	0.8±1.0	0.9±0.8	1.1±0.9
Preimplantation loss (%)	0.3±1.4	1.6±3.3	1.3±2.7	0.7±1.7

Necropsy examination on F_1 pups: Necropsy examination showed bilateral hydronephrosis in one low dose dam. No abnormal findings were noted in the other dams. Necropsy findings in other F_1 animals are summarized in the table below. These changes were not considered as drug-related since no dose-dependence was seen

Abnormal necropsy findings in F_1 pups

Dosage (mg/kg)	Vehicle	6	30	120
Total pups affected		2	3	
Total litters affected		2	3	
Bilateral hydronephrosis		1		
Bilateral hyperplasia of the testes		1	1	
Hyperplasia of the uteri and ovaries			2/2*	
Hydronephrosis of the right kidney and dilatation of the renal pelves of the left kidney			1	

* fetuses/litters

In summary, WAL 801 CL was given orally (by gavage) at 6, 30 and 120 mg/kg/day to male rats for a 10-week pre-mating period, and to female rats during a 2-week pre-mating period, during the 3-week gestation period, and during the 3-week lactation period. Treatment-related toxicity in the HD animals included decreased body weight gain and food consumption. Mating index was similar in all groups. However, the fertility index (pregnant rate) was decreased in HD animals, which might be related to the slight irregularities of the estrous cycles. Histological examination showed no changes in spermatogenesis, suggesting that the reduced conception rate was not due to male infertility. In HD group, fetus body weight, pup body weight, and pup body weight gain during lactation day 1 to day 21 were decreased. A slight retardation in erection of the pinnae, fur growth, and opening of the eyes was noted in HD pups. Dosing at 120 mg/kg did not impair rats' ability to litter and rear their pups. The fertility of F_1 animals was not affected. There was no drug-related embryotoxicity or teratogenicity. The NOAEL for fertility and general reproductive performance in this study was 120 mg/kg for males and 30 mg/kg for females. The NOAEL for maternal toxicity was 30 mg/kg.

U82-0063: Teratogenicity of WAL 801 CL in rats. Vol. 20, Page 209

Key study findings: WAL 801 CL at HD (200 mg/kg) caused mortality in pregnant rats. There was no evidence of teratogenicity at any dose level. The NOAEL was considered to be 35 mg/kg for dams, and 200 mg/kg for embryo-fetal development.

Document #: U82-0063
Study No: B95
Conducting laboratory and location: Reproduction Section, Department of Experimental Pathology and Toxicology, Boehringer Ingelheim KG, D-6507 Ingelheim am Rhein
Date of study initiation: August 1982
GLP compliance: Yes
QAU: Yes
Animal: Female rats/Chbb:THOM (SPF), 10-week old, 246 g, 23/group
Route: Oral (gavage)
Drug: WAL 801 (Batch #: II) in distilled water
Study design:

Group		Dose (mg/kg)	N (main study)	Dose volume (ml/kg)
1	Control	Vehicle	23	0.5
2	Low dose	6	23	0.5
3	mid dose	35	23	0.5
4	High dose	200	23	0.5

The purpose of this study was to determine the potential toxic effects of WAL 801 CL on pregnant rats and embryo-fetal development. Female rats were mated with males in the ratio of 1 male: 2 females, and the day positive mating observed (a vaginal plug or sperm) was designated as gestation day 1. Pregnant rats were treated from gestation day 7 through day 16. On gestation day 22 terminal, cesarean section was performed. Toxicity was assessed as shown below.

Dams:
Mortality and clinical observations: Pregnant days 1, 7 to 16, and 22
Body weights: Pregnant days 1, 7 to 16, and 22
Postmortem examination: The animals were sacrificed on pregnant day 22. Necropsy was performed on all animals, and the number of corpora lutea was determined.

Fetuses:
Opening the uterus: The numbers of living fetuses, dead fetuses, and early and late resorptions were determined. The litter, fetal and placental weights were also determined. Each fetus was examined for external malformations.
Skeletal examination: Two-thirds of the living fetuses of each litter
Visceral examination: The remaining one-third of the fetuses

Results:

Mortality and clinical observations: No treatment-related effects were noted in LD and MD animals. In HD group, 5 animals died during the 10-day dosing period. Histopathological examination showed shock lungs (hyperemia and edema) and myocardial injury, indicating these animals died of shock and acute heart failure. Clinical signs observed in the HD animals included severe agitation, retching, pilo-erection, and sedation. The animals appeared weak. One to two days after the last dosing, the conditions of these animals returned to normal.

Body weight changes: A reduction in body weights and body weight gain was noted in HD rats (see table below). Body weight parameters were unaffected by treatment at doses ≤ 35 mg/kg. No gravid uterine weights were provided.

Body weight changes in pregnant rats treated with WAL 801 CL (g, mean ± SD)

Group	mg/kg	Day 7	Day 16	Day 22	BW Δ Days 7-16
1	0	272.6±10.6	321.2±16.1	400.6±36.0	48.6
2	6	273.3±13.3	322.9±15.4	402.1±29.8	49.6
3	35	267.5±14.0	312.1±18.4	389.3±27.4	44.6
4	200	272.0±19.3	296.1±16.7	383.1±24.6	24.1

Post-mortem examinations:

Necropsy observations: No abnormal findings were noted in the animals sacrificed on pregnant day 22. One LD animal died because of the dosing accident. For the five HD animals died during the treatment period, treatment-related findings noted in the lungs included mottled color of the surface, and very wet cut surface. The lungs and hearts of three animals were examined histopathologically. The positive findings were shock lungs (hyperemia with interalveolar perivascular edema) and myocardial injury (necrosis or eosinophilia of individual myocardial fibers and pronounced interstitial edema).

Reproductive parameters: Reproductive parameters are summarized in the table below. No toxicologically significant, treatment-related positive findings were noted.

Summary of maternal and fetal data at cesarean section (mean ± SD)

Dosage (mg/kg)	Vehicle	6	35	200	Historical control (73-77)	Historical control (77-79)
Female mated	23	23	23	23		
Died	0	1	0	5		
Pregnant survivors	21	19	17	15		
Aborted	0	0	0	0		
Pregnant at C-section	21	19	17	15		
Corpora lutea/animal	13.9±2.7	15.1±2.3	14.1±1.9	14.9±2.1	14.3 (13.3-15.4)	14.6 (12.8-16.4)
Implantation/animal	13.0±3.2	13.9±4.1	12.0±3.8	13.3±3.6	13.7 (12.4-15.0)	13.7 (12.1-15.4)
Resorptions/dam	0.9±1.1	1.5±2.0	0.4±0.6	1.5±1.4	1.0 (0-2.0)	1.2 (0-2.4)
Preimplantation loss (%)	3.9±7.1	1.8±9.7	8.2±10.8	5.3±8.7	1.9 (0-6.2)	3.1(0-7.9)
Postimplantation loss (%)	3.6±4.0	5.1±5.9	0.8±2.1	5.9±4.6	3.8 (0-9.3)	5.4(0-13.0)
Dead fetuses	0	0	0	0	0	0
Total viable fetuses	253	235	198	177		
Viable fetuses/dam	12.0±3.4	12.4±3.7	11.6±3.6	11.8±2.8	12.7 (11.0-14.4)	12.5 (11.1-14.0)
Viable male fetuses (%)	57	51	53	55		
Fetal body weights, (g)	5.27±0.33	5.27±0.20	5.38±0.25	5.16±0.24	5.2 (5-5.4)	5.25 (4.98-5.52)
Placental weights (g)	0.47±0.07	0.45±0.05	0.43±0.04	0.47±0.04		

Fetal examinations: A total of 863 fetuses were available for examination. After macroscopic appraisal of all fetuses, 570 were examined for skeletal anomalies and 293 for internal anomalies. Positive findings of malformations and variations are summarized in the table below. The incidence of these positive findings was very low. There was no dose-dependence. In addition, some findings (hydrocephalus, cleft plate, kinked tail, dilatation of renal pelvis, and absence of asymmetric sternebrae) were also found in the vehicle control group or recorded in the historical data. Therefore, the reviewer does not consider these findings are toxicologically significant.

Summary of malformation and variation data at cesarean section (mean ± SD)

Dosage (mg/kg)	Vehicle	6	35	200	Historical control (73-77)	Historical control (77-79)
Litters evaluated	21	19	17	15	378	303
Fetuses evaluated	253	235	198	177	4800	3799
Total malformations	**1**	**1**	**2/2***	**2/2**	**12**	**15**
Hydrocephalus	1	0	0	1		1
Dextrorotation of the heart	0	1	0	0		
Cyclopia	0	0	1	0		
Cleft plate	0	0	0	1	1	
Kinked tail	0	0	1	0		
Malformations/dam	0.1±0.2	0.1±0.2	0.1±0.3	0.1±0.4	0 (0-0.2)	0.1 (0-0.2)
Malformation in % viable fetuses	0.1±1.8	0.1±1.4	0.2±1.8	0.4±3.2	0.1 (0-0.2)	0.1 (0-0.2)
Total variations	**1**	**1**	**2/2**	**1**		**26**
Dilatation of renal pelvis	1	0	2/2	1		8
Absent of asymmetric sternebrae	0	1	0	0		3
Variations/dam	0.1±0.2	0.1±0.2	0.1±0.3	0.1±0.3	0 (0-0.2)	0.1 (0-0.2)
Variations in % viable fetuses	0.1±1.3	0.1±1.1	0.3±2.4	0.3±4.1	0.1 (0-0.2)	0.2 (0-0.7)

* fetus/litter

In summary, pregnant rats were treated with WAL 801 CL by gavage from gestation days 7 to 16 at doses of 6, 35, and 200 mg/kg. Mortalities were noted at 200 mg/kg (5/23). Clinical signs in these animals included severe agitation, retching, pilo-erection, and sedation. The cause of the deaths was heart and pulmonary failure. Decreased body weight gain was observed in animals treated at 200 mg/kg. Regarding reproductive effects, no toxicologically significant findings were noted. A few malformations and variations were noted in control and treated animals. Because of the low incidence and lack of the dose-dependence, these changes were not considered as biologically relevant. The NOAEL was considered to be 35 mg/kg for dams, and 200 mg/kg for embryo-fetal development.

U84-0243: Teratogenicity of WAL 801 CL in rabbits. Vol. 20, Page 312

Key study findings: WAL 801 CL at HD (75 mg/kg) caused embryotoxicity evidenced by total resorption in 3 pregnant rabbits. Abortion was noted in 1 animal at 75 mg/kg. There was no evidence of teratogenicity at any dose level. The NOAEL was considered to be 15 mg/kg for dams, and 75 mg/kg for embryo-fetal development.

Document #: U84-0243
Study No: C 08
Conducting laboratory and location: Reproduction Section, Department of Experimental Pathology and Toxicology, Boehringer Ingelheim KG, D-6507 Ingelheim am Rhein
Date of study initiation: June 13, 1983
GLP compliance: Yes
QAU: Yes
Animal: Female rabbits/Chbb:HM, 5-6 months old, 2437 g, 18/group
Route: Oral (gavage)
Drug: WAL 801 (Batch #: IV) in distilled water
Study design:

Group		Dose (mg/kg)	N	Dose volume (ml/kg)
1	Control	Vehicle	18	1
2	Low dose	5	18	1

3	mid dose	15	18	1
4	High dose	75	18	1

The purpose of this study was to determine the potential embryolethal, fetotoxic, or teratogenic effects of WAL 801 CL in pregnant rabbits. Female rabbits were mated with males from the same brood twice at an interval of 1 hr, and the day that positive mating observed (sperm detected in the vaginal smear) was designated as gestation day 0. Pregnant rabbits were treated once daily from gestation day 6 through day 18. On gestation day 29 terminal cesarean section was performed. Toxicity was assessed as shown below.

Dams:
Mortality and clinical observations: All animals, entire test period
Body weights: Daily during the treatment period, and on the last day of pregnancy
Postmortem examination: The animals were sacrificed on pregnant day 29. Necropsy was performed on all animals. The fetuses were removed by hysterectomy. The number of corpora lutea was determined.

Fetuses:
Opening the uterus: The numbers of living fetuses, dead fetuses, and early and late resorptions were determined. The litter, fetal and placental weights were also determined. Each fetus was examined for external malformations.
Visceral examination: All fetuses, 24 hr after being kept in the incubator
Skeletal examination: All fetuses, with a [redacted] X-ray instrument

Results:

Mortality and clinical observations: No treatment-related effects were noted. One control animal died of dosing accident on day 5 of dosing. One LD animal was sacrificed because of fracture of the tibia and fibula of the right rear leg following the 2nd dosing. In HD group, one animal aborted on day 21 of pregnancy. The sponsor indicated that this abortion might not be treatment-related since in historical control, abortion occurred occasionally in this strain of rabbits (2 of 286, 1973 to 1977; 5 of 165, 1977 to 1979).

Body weight changes: An increase in body weight gain was noted in treated groups at the end of the treatment period (day 18 of pregnancy, see table below). However, the mean body weights between treated and control animals were similar at the end of the treatment period (pregnancy day 18) and at the end of the pregnancy period (day 29). Therefore, the increased body weight gain observed in the treated groups might not be toxicologically significant.

Body weight changes in pregnant rabbits treated with WAL 801 CL (g, mean ± SD)

Group	mg/kg	Day 6	Day 18	% control	BW Δ Days 6-18	Day 29	% control
1	0	2485.7±92.4	2512.9±93.4	100	27.2	2697.9±150.8	100
2	5	2448.5±140.1	2493.1±121.3	99.2	44.6	2643.8±150.0	98.0
3	15	2462.8±139.4	2525.0±126.7	100.5	62.2	2661.1±170.2	98.6
4	75	2472.9±132.0	2558.6±123.7	101.8	85.7	2660.7±108.6	98.6

Post-mortem examinations:

Necropsy observations: One HD animal showed hyperplasia of the left kidney and acute abscessing pyelonephritis. No other possibly drug-related abnormal findings were noted.

Reproductive parameters: Reproductive parameters are summarized in the table below. Total resorptions occurred in 3 HD animals. No other toxicologically significant, treatment-related positive findings were noted.

Summary of maternal and fetal data at cesarean section (mean ± SD)

Dosage (mg/kg)	Vehicle	5	15	75	Historical control (73-77)	Historical control (77-79)
Female mated	18	18	18	18	286	165
Died	1	1	0	0	1	3
Total resorptions	0	0	0	3		
Aborted	0	0	0	1	2	5
Pregnant survivors	14	13	18	14	265	138
Corpora lutea/animal	9.6±2.3	8.0±1.2	9.7±2.7	8.1±2.0	8.0 (7.0-9.1)	8.2 (6.4-9.9)
Implantation/animal	8.1±2.7	6.2±2.5	7.9±2.3	6.7±1.7	7.5 (6.3-8.6)	6.8 (5.7-8.0)
Resorptions/dam	0.6±0.7	0.8±0.9	1.3±1.8	1.0±1.5	0.5 (0-1.1)	0.7 (0-1.7)
Preimplantation loss (%)	9.9±9.5	14.9±13.9	10.5±9.1	10.4±7.7	3.6 (0-11.2)	11.0 (0-24.0)
Postimplantation loss (%)	4.2±5.8	8.8±9.7	8.9±13.8	6.7±11.4	2.8 (0-7.3)	4.9 (0-16.6)
Dead fetuses	0	0	0	0	0	2
Total viable fetuses	104	71	119	80	1848	844
Viable fetuses/dam	7.4±2.7	5.5±2.8	6.6±3.0	5.7±2.1	7.0 (5.8-8.1)	6.1 (5.0-7.3)
Viable male fetuses (%)	52	37	55	50	49	49
Postnatal mortality (0-24 hr)	4 (3.8%)	2 (2.8%)	6 (5.0%)	2 (2.5%)		
Fetal body weights, (g)	37.28±7.22	41.98±4.18	40.06±4.81	40.23±4.62	38.31 (35.48-41.14)	38.40 (35.84-40.95)
Placental weights (g)	5.08±0.87	5.55±1.01	5.40±1.15	5.25±0.72		

Fetal examinations: A total of 374 fetuses were available for examination. The fetuses died within the 1st 24 hr post partum showed no pathologic findings in macroscopic examination. The positive findings of malformations and variations are summarized in the table below. The incidence of these positive findings was low. There was no dose-dependence. The malformations were only noted in MD group. In addition, some findings were also found in the vehicle control group or recorded in the historical data. Therefore, the reviewer does not consider these findings are toxicologically significant.

Summary of malformation and variation data at cesarean section (mean ± SD)

Dosage (mg/kg)	Vehicle	5	15	75	Historical control (73-77)	Historical control (77-79)
Litters evaluated	14	13	18	14	265	138
Fetuses evaluated	104	71	119	80	1848	844
Total fetuses with malformations	**0**	**0**	**3/3***	**0**	**66**	**7**
Synostosis of sternebrae	0	0	3/3 (2.5%)	0	3? (0.16%)	1?(0.1%)
Absence of gallbladder	0	0	1 (0.84%)	0	2 (0.1%)	3 (0.36%)
Malformations/dam	0	0	0.2±0.4	0		
Malformation in % viable fetuses	0	0	0.4±2.3	0		
Total fetuses with variations	**2/2**	**1**	**4/3**	**1**	**62**	**39**
Absence of the 12th rib	0	0	0	1 (1.25%)		1 (0.1%)
13th rib	1 (0.96%)	0	1 (0.84%)	0		7 (0.83%)
Dilatation of renal pelvis	1 (0.96%)	0	0	0		
Flexure of fore paw	1 (0.96%)	0	2/1 (1.68%)	0		7 (0.83%)
Absence of accessory lobe of lung	0	1 (1.41%)	1 (0.84%)	0		22 (2.61%)
Variations/dam	0.1±0.4	0.1±0.3	0.2±0.5	0.1±0.3		
Variations in % viable fetuses	0.4±2.5	1.5±17.8	0.4±2.3	0.1±1.1		

* fetus/litter

In summary, pregnant rabbits were treated with WAL 801 CL by gavage from gestation days 6 to 18 at doses of 5, 15, and 75 mg/kg. No drug-related mortality, clinical signs, and body weight changes were noted. Abortion was noted in one HD animal. Total resorptions were observed in 3 HD animals. Malformations were seen in 3 MD fetuses, and variations were noted in control and treated animals. Because of the low incidence and lack of the dose-dependence, these changes were not considered as biologically relevant. The NOAEL was considered to be 15 mg/kg for dams, and 75 mg/kg for embryo-fetal development.

U87-0806: Perinatal and postnatal study (Segment III) in rats (oral administration). Vol. 24, Page 337

Key study findings: Maternal toxicity was noted in the HD animals that included clinical signs, decreased body weight gain and food consumption. Abortion was noted in one HD animal. No toxicologically significant abnormal findings were noted regarding F_0 reproductive parameters, F_1 development and behavioral parameters, and F_1 fertility parameters. The NOAEL for perinatal and postnatal development in this study was 120 mg/kg. The NOAEL for maternal toxicity was 30 mg/kg.

Document #: U87-0806
Study No: C43, A0000938
Conducting laboratory and location: Reproduction Section, Department of Experimental Pathology and Toxicology, Boehringer Ingelheim KG, D-6507 Ingelheim am Rhein, Germany
Date of study initiation: August 18, 1986
GLP compliance: Yes
QAU: Yes
Animal: Timed-pregnant female rats/Chbb:THOM (SPF), 24/group
Route: Oral (gavage)
Drug: WAL 801 (Batch #: X) in distilled water
Study design:

Group		Dose (mg/kg)	N/sex (main study)	Dose volume (ml/kg)
1	Control	Vehicle	24	5
2	Low dose	6	24	5
3	mid dose	30	24	5
4	High dose	120	24	5

The purpose of this study was to determine the potential toxic effects of WAL 801 CL on the pregnant and lactating rats and on the development of the offspring following daily treatment (by gavage, 6, 30 and 120 mg/kg) from gestation day 16 through lactation day 21. Toxicity was assessed as shown below.

Dams:
Mortality and clinical observations: Daily
Body weights: Daily
Food consumption: Weekly

F_1 generation observations:
Pup number, weight, sex, macroscopical examination: At birth

On day 4 of lactation, the litters were culled to 4/sex/litter. These pups were reared until day 21 of lactation. The following measurements were performed:
Erection of ears: Days 4 and 5
Beginning of fur growth: Days 6 and 7
Free running: Days 12 and 13
Eruption of the upper incisors: Days 13 and 14
Opening of the eyes: Days 15 and 16
After weaning, the litters were culled again to 1/sex/litter. These animals were subjected to behavioral tests:
Swimming test: Week 4
Hearing test: Week 4
Pupillary test: Week 4
Water maze test: Week 5

F_1 generation reproductivity:
At the 10^{th} week of life, F_1 animals were mated within the dose groups. Mating siblings was avoided. The mated females were terminated between pregnancy days 13 and 16, and the numbers of corpora lutea, living fetuses, dead fetuses, and resorptions were determined. F_1 males were also terminated and autopsied.

Results:

Mortality and clinical observations: One MD animal died due to faulty gavage. No treatment-related mortality was noted. One MD animal and three HD animals had slight crepitant respiratory sounds for several days. One HD animal had a reddish encrusted nasal secretion. One HD animal chewed the cage bedding. Miscarriage was noted in one HD animal. Generally, the drug was well tolerated in LD and MD animals. The number of non-pregnant rats was 6, 3, 7, and 5 in control, LD, MD, and HD groups, respectively.

Body weight changes: From gestation day 16 to day 22, HD animals showed less body weight gain (52.7 g, ↓17%) than in control animals (69.0 g). During the lactation phase, there was a dose-dependent decrease in body weight gain (see table below). However, in both pregnancy and lactation phases, there were not great differences in the final body weights among different groups.

Body weight changes in rats treated with WAL 801 CL during lactation phase (g, mean ±SD)

Treatment	Day 1	Day 20	% control	Gain (days 1-20)	% control
Control	269.8±12.0	302.2±14.5	100	32.4	100
6 mg/kg	269.3±12.3	299.5±11.9	99.1	30.2	93.2
30 mg/kg	263.5±13.4	291.2±16.6	96.4	27.7	85.5
120 mg/kg	267.3±17.8	292.1±16.4	96.7	24.8	76.5

Food consumption: Weekly food consumption was decreased in HD animals during treatment period (see table below).

Weekly food consumption in rats treated with WAL 801 CL (g, mean ±SD)

Dosage (mg/kg)	Vehicle	6	30	120
Gestation Week 3	184.1±11.8	185.2±13.0	181.7±13.1	164.7±15.6
Lactation phase	351.7±27.4	356.1±28.2	344.2±43.6	342.6±46.5

Postmortem examinations of dams: The dams were terminated after weaning of the pups. One HD animal showed a diffuse nodular thickening in the liver and an enlarged spleen. Histopathologic examination showed multifocal intra-hepatic bile duct proliferation and focal cystic bile ducts, and high-grade congestion in the spleen.

Delivery and lactation parameters: The table below summarizes the delivery and lactation data. No drug-related, toxicologically significant changes were noted.

Summary of delivery and lactation parameters (mean ± SD)

Dosage (mg/kg)	Vehicle	6	30	120
Total animals used	24	24	24	24
Animals pregnant	18	21	17	19
Aborted				1
Natural delivery	18	21	17	18
Gestation period (days)	22.1±0.2	22.1±0.3	22.0±0	22.0±0
Stillbirths	1	3	1	3
Stillbirth/dam	0.1±0.2	0.1±0.5	0.1±0.2	0.2±0.5
Total live pups on day 1	198	237	197	214
Live pups/dam on day 1	11.0±2.8	11.3±3.1	11.6±2.9	11.9±3.3
Male pups (%)	55	49	46	46
Dead pups on days 1-4	4	2	4	8
Pup loss % days 1-4	0.3±1.8	0.1±0.7	0.6±2.0	0.7±3.0
Viability index (days 1-4, %)	98	99.2	98	96.3
Dead pups on days 4-21	1	1	3	1
Pup loss % days 4-21	0±0.7	0±0.7	0.3±2.3	0±0.7
Weaning index (days 4-21, %)	99.5	99.6	98.4	99.5
Total dead pups (days 1-21)	5	3	7	9
---Cannibalism	2	1	4	5
---Starvation	3	1	2	4
---Unknown	0	1	1	0
Pup body weight on day 1, (g)	6.06±0.57	6.17±0.37	6.22±0.25	6.06±0.35
Pup body weight on day 21, (g)	36.40±3.57	37.12±3.94	36.35±4.34	35.48±3.84
Body weight gain days 1-21 (g)	30.34±3.63	30.96±3.69	30.13±4.28	29.42±3.96
Malformation	0	0	0	1(hydronephrosis)
Variations	0	0	0	0

Parameters of development and behavior of F_1 generation: No toxicologically significant findings in development and behavioral parameters were observed. Similar results were seen between control and treated groups.

Fertility test on the F_1 generation: The test of fertility (1 male and 1 female per litter within the same dose group, but sibling mating was avoided) was carried out at the age of 10 weeks. Results are summarized in the table below. There were no drug-related, toxicologically significant abnormal findings regarding fertility of the F_1 generation.

Summary of reproductive parameters of F_1 generation (mean ± SD)

Dosage (mg/kg)	Vehicle	6	30	120
Females mated	17	21	17	18
Mating index (%)	100	100	100	100
Females pregnant	17	21	16	17
Fertility index (%)	100	100	94	94
Maternal death	0	0	0	0
Aborted	0	0	0	0
Total resorption	0	0	0	0
Natural delivery	0	0	0	0
Pregnant at C-section (day 14)	17	21	16	17
Total corpora lutea	266	354	261	279
Total implantation	262	349	248	267
Total live fetuses	242	312	239	250
Total resorptions	20	37	9	17
Corpora lutea/animal	15.6±1.9	16.9±1.7	16.3±1.6	16.4±2.3
Implantation/animal	15.4±1.8	16.6±1.8	15.5±2.9	15.7±3.6
Live fetuses/dam	14.2±2.1	14.9±2.4	14.9±2.8	14.7±3.5
Resorptions/dam	1.2±1.4	1.8±2.4	0.6±0.8	1.0±1.1
Preimplantation loss (%)	0.2±1.4	0.3±1.3	1.3±5.1	1.0±5.5
Postimplantation loss (%)	4.3±3.9	6.3±5.0	1.5±2.3	3.7±5.1

In summary, WAL 801 CL was given orally (by gavage) at 6, 30 and 120 mg/kg/day to pregnant rats from gestation day 16 to lactation day 21. Treatment-related toxicity was noted in the HD animals that included clinical signs, decreased body weight gain and food consumption. Abortion was noted in one HD animal. No toxicologically significant abnormal findings were noted regarding F_0 reproductive parameters, F_1 development and behavioral parameters, and F_1 fertility parameters. The NOAEL for perinatal and postnatal development in this study was 120 mg/kg. The NOAEL for maternal toxicity was 30 mg/kg.

U96-0244: Single dose toxicity study of WAL 801 CL in new-born rats by oral administration. Vol. 36, Page 082

Key study findings: Mortality occurred at ≥ 80 mg/kg. Rolling-like convulsions were noted in all treated groups and lasted for 1 hr after dosing. Clinical signs including irregular respiration, bradypnea, hypothermia, cyanosis or poor suckling were noted at ≥ 20 mg/kg. No NOAEL was determined.

Document No: U96-0244
Study #: E9301, A0000913
Conducting laboratory and location: Kawanishi Pharma research Institute, Department of Experimental Pathology, Nippon Boehringer Ingelheim Co., Ltd., 3-10-1 Yato, Kawanishi, Hyogo, Japan
Date of study initiation: Not indicated.
GLP compliance: Yes
QA report: Yes
Animal: Rats/Crj:CD (SD), 4 days old, 8/group (12 pups in control group)
Route: Oral by gavage
Dosage: 0, 10, 20, 40, 80, 160, and 320 mg/kg (dosing volume: 10 ml/kg).
Drug: WAL 801 CL (Batch #: XII, purity: [redacted], dissolved in distilled water
Dosing regimen: Single dose

The purpose of this study was to determine the acute toxicity of WAL 801 CL in new-born rats after a single oral administration.

Observations and times:

Clinical signs:	Immediately after dosing, and 5, 15, and 30 min, 1, 3, and 6 hr after dosing, and once daily thereafter for 14 days
Body weights:	Daily
Necropsy:	All animals

Results:

Mortality: Mortality occurred at the doses of 80 mg/kg and higher.

Mortality data in rats treated orally with WAL 801 CL

Dose (mg/kg)	80	160	320
Within 6 hr		1	1
7-24 hr	2	2	2
Days 2-7	0	5	3
Total	2	8	6*

* Two extra rats died from dosing mistake.

Clinical observations: Rolling-like convulsions were noted in all treated groups and lasted for 1 hr after dosing. Clinical signs including irregular respiration, bradypnea, or poor suckling were noted at ≥ 20 mg/kg. Hypothermia, cyanosis, emaciation and gasping were noted at ≥ 80 mg/kg.

Body weights: No treatment-related effects on body weight changes were noted at 10 and 20 mg/kg. Body weight gain in animals at ≥ 40 was decreased in the 1st few days following dosing (see table below).

Body weight gain in rats treated with a single dose of WAL 801 CL (g, mean ± SD)

Dose (mg/kg)	Day 0, (BW)	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14
Control	10.7±0.7	1.7±0.5	3.8±0.8	5.9±0.7	8.4±1.0	16.0±1.8	35.2±3.9
10	10.6±0.9	1.9±0.4	3.7±0.6	5.6±0.9	8.0±1.2	15.7±1.7	33.4±3.7
20	10.4±0.5	1.6±0.5	3.5±0.7	5.4±1.1	7.7±1.2	15.3±2.0	33.0±5.6
40	10.8±0.6	1.0±0.5	2.6±0.6	4.7±0.9	6.9±1.0	14.3±1.6	32.1±3.8
80	10.9±0.5	-0.8±0.3	0.3±0.4	2.0±0.8	4.1±1.3	11.5±2.4	28.2±4.8
160	10.4±0.5	-0.7±0.2	-1.3±0.3				
320	10.6±1.0	-0.7±0.3	-1.5±0.8				

Necropsy: No abnormal findings were noted in the surviving pups. In the pups that died after dosing, distention of the urinary bladder and a slight dilatation of renal pelvis or ureter were observed.

In summary, new-born rats were treated with a single oral dose of WAL 801 CL at 10 to 320 mg/kg. Mortality was observed at 80 mg/kg and higher. The new-born rats seemed more sensitive to the drug. Clinical signs including irregular respiration, bradypnea, hypothermia, cyanosis or poor suckling were noted at ≥ 20 mg/kg. No NOAEL was determined.

Reproductive and developmental toxicology summary and conclusions:

In the combined fertility and, embryo-fetal, pre- and post-natal development reproduction study in rats (doses = 6, 30 and 120 mg/kg/day), the fertility index (pregnant rate) was decreased in HD animals, which might be related to the slight irregularities of the estrous cycles. Histological examination showed no changes in spermatogenesis, suggesting that the reduced conception rate was not due to male infertility. In HD group, fetus body weight, pup body weight, and pup body weight gain during lactation day 1 to day 21 were slightly decreased. A slight retardation in erection of the pinnae, fur growth, and opening of the eyes was noted in HD pups. Dosing at 120 mg/kg did not impair rats' ability to litter and rear their pups. The fertility of F_1 animals was not affected. There was no drug-related embryotoxicity or teratogenicity. The NOAEL for fertility and general reproductive performance in this study was 120 mg/kg for males and 30 mg/kg for females.

In the embryo-fetal development study in rabbits (doses = 5, 15 and 75 mg/kg/day), abortion was noted in one HD animal. Total resorption was observed in 3 HD animals. Malformations were seen in 3 MD fetuses, and variations were noted in control and treated animals. Because of the low incidence and lack of the dose-dependence, these changes were not considered as biologically relevant. The NOAEL was considered to be 15 mg/kg for dams, and 75 mg/kg for embryo-fetal development.

In the embryo-fetal development study in rats (doses = 6, 35, and 200 mg/kg/day), maternal toxicity (mortality, clinical signs in these animals included severe agitation, retching, pilo-erection, and sedation. The cause of the deaths was heart and pulmonary failure. Decreased body weight gain was observed in animals treated at 200 mg/kg. Regarding F_1 generation, no toxicologically significant findings were noted. A few malformations and variations were noted in control and treated animals. Because of the low incidence and lack of the dose-dependence, these changes were not considered as biologically relevant. The NOAEL was considered to be 35 mg/kg for dams, and 200 mg/kg for embryo-fetal development.

In the oral pre- and postnatal development study in rats (doses = 6, 30, and 120 mg/kg/day), abortion was noted in one HD animal. No toxicologically significant abnormal findings were noted regarding F_0 reproductive parameters, F_1 development and behavioral parameters, and F_1 fertility parameters. The NOAEL for perinatal and postnatal development in this study was 120 mg/kg. The NOAEL for maternal toxicity was 30 mg/kg.

In the toxicity study conducted in new-born rats (doses = 10-320 mg/kg/day), mortality was observed at 80 mg/kg and higher. The new-born rats seemed more sensitive to the drug. Clinical signs including irregular respiration, bradypnea, hypothermia, cyanosis or poor suckling were noted at ≥ 20 mg/kg. No NOAEL was determined.

Labeling review:

Epinastine had no effect on fertility of male rats. *Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MROHD.*

Pregnancy: Teratogenic Effects: Pregnancy Category C

In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was *approximately 150*,000 times the MROHD. *Total resorptions* and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was *approximately 55*,000 times the MROHD. *In both studies, no drug-induced teratogenic effects were noted.*

Epinastine reduced pup body weights and body weight gain [redacted] following an oral dose [redacted]

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, [redacted] ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [redacted] ophthalmic solution is administered to a nursing woman.

VIII. SPECIAL TOXICOLOGY STUDIES:

OCULAR TOXICITY STUDIES

Studies reviewed:

TX00032: Epinastine: A six-month ocular toxicity study in rabbits. Vol. 18, Page 050
TX00033: Epinastine: A six-month ocular toxicity study in monkeys. Vol. 18, Page 144
U93-0709: 4-week local ocular tolerance study of WAL 801 CL eye drops by instillation into the conjunctival sac of rabbits. Vol. 35, Page 001
U97-2105: Epinastine (WAL 801 CL): 4-week local ocular tolerance study of WAL 801 CL eye drops by instillation into the conjunctival sac of rabbits. Concentrations in aqueous humor and plasma on day 28. Vol. 36, Page 108
U93-0782: Acute eye irritation study with "stressed" WAL 801 CL eye drops (0.1%), containing 0.5% WAL 2003 by instillation into the conjunctival sac of rabbits. Vol. 35, Page 217
U95-0510: 13-week local ocular tolerance study with WAL 801 CL eye drops by instillation into the conjunctiva sac of rabbits. Vol. 35, Page 360
U96-0105: 4-week local ocular tolerance study of WAL 801 CL eye drops by instillation into the conjunctival sac of rabbits. Vol. 36, Page 001

TX00032: Epinastine: A six-month ocular toxicity study in rabbits. Vol. 18, Page 050

Key study findings: Ocular topical treatment with epinastine HCl ophthalmic solution (0.05%, 0.1% and 0.5%) to NZW rabbits (tid x 6 months) induced no significant ocular and systemic toxicity.

Study №: TX00032
Study Location: Allergan, 2525 Dupont Drive, Irvine, CA 92612

Study Initiate Date: 6/29/2000
Compliance with GLP/QAU: Yes
Study Aim: To determine the ocular toxicity of epinastine HCl ophthalmic solution following tid topical ocular administration to New Zealand white rabbits for 6 months followed by a 1-month recovery period.
Compound/Vehicle: 0.05%, 0.1%, and 0.5% epinastine HCl ophthalmic solution; the composition of drug and vehicle is listed in the following table, which was similar to the clinical formulation.

Ingredient (% w/v)	Vehicle Lot # 11764	0.05% epinastine HCl Lot # 11765	0.1% epinastine HCl Lot # 11766	0.5% epinastine HCl Lot # 11767
Formulation #	9342X	9343X	9347X	9346X
Epinastine HCl	0	0.05	0.1	0.5
Benzalkonium chloride	0.01	0.01	0.01	0.01
Edetate disodium, USP				
Monobasic sodium phosphate dihydrate				
Sodium chloride				
Purity				

Dose & Route: One drop (35 μl)/eye, left eyes only, tid (at 3-hr intervals) for 6 months.
Animals: New Zealand white rabbits, 3-5 months old, weighing 2.25-2.95 kg; 12/sex/group
Study Design: Epinastine HCl ophthalmic solution or vehicle was applied to the left eye (1 drop/35 μl/eye) of each rabbit tid for 6 months as shown in the following table.

Group	Epinastine HCl	# of Animals	Treatment Frequency	Dosing Duration (Days)
1	Vehicle	12/sex/group Main study: 8/sex; Recovery: 4/sex	tid	6 months
2	0.05%			
3	0.1%			
4	0.5%			

The following parameters were monitored.

Mortality: 2x/day
Clinical observations: 1x/day
Gross ocular observations: At least 2x/day
Biomicroscopic examination: Pretreatment, Weeks 14 and 27, and at the end of the recovery period
Indirect ophthalmoscopic examination: Pretreatment, Weeks 14 and 27, and at the end of the recovery period
Pupillary reflex: Pretreatment, Weeks 14 and 27, and at the end of the recovery period
Ocular discomfort (blinking and/or squinting, closure of the eye, and repeated pawing or rubbing): At 10 min after the 1st dosing during the 1st week of each week during the treatment period
IOP: Pretreatment, Weeks 12 and 26, and at the end of the recovery period
Body weights: Weekly
Food consumption: One day per week
Clinical pathology: Pretreatment, Weeks 12 and 26, and at the end of the recovery period
Necropsy: All animals
Organ weights: The following tissues and organs from all animals were weighted: adrenal glands, brain, kidneys, liver, heart, ovaries, spleen, testes, and thymus.

Histopathology: The ocular tissues from all animals were observed histopathologically. In addition, tissues (prostate, seminal vesicle, kidney, adrenal, peritoneum, lung, skin, and testis) with gross lesions, and buccal and masseteric glands from 6 males each from the control and HD groups were evaluated microscopically.
PK/TK: Days 26 and 175. Blood samples were collected from 4/sex animals in all groups prior to the 3rd daily dosing, and at 0.5, 1, 2, 3, 4, 6, and 8 hr post the last dose.

Results:

Mortality and clinical observations: No death occurred during the treatment period. No remarkable clinical signs attributed to topical ocular treatment with epinastine were noted.

Gross ocular observations: Transient, minimal ocular hyperemia was noted in all groups with a slightly higher incidence (5%) in HD animals relative to the control animals (1% in females and 2% in males). This change was not considered as toxicologically significant because of the low incidence and severity. No other biologically relevant changes were noted.

Biomicroscopic examination, indirect ophthalmoscopic examination, and pupillary reflex examination: No toxicologically significant, treatment-related changes were noted. Mild to moderate conjunctival congestion was observed in the treated and/or untreated eyes of 10, 12, 8 and 10 of 24 rabbits in Groups 1, 2, 3, and 4. This finding was not considered toxicologically significant because the congestion occurred in equal or greater incidence in the untreated control eyes (see table below).

Incidence of conjunctival congestion in rabbits treated with epinastine HCl ophthalmic solution

	Males								Females							
Group	1		2		3		4		1		2		3		4	
3 months	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD
Mild	1		3	3		2	3	3					2			
Moderate		1														
6 months																
Mild	1	3		5		3	1	3	2	5	2	4		2	2	4
Moderate		1							1							

IOP – No treatment-related changes were noted.

Ocular discomfort: Transient, minimal to mild ocular discomfort was noted in all groups (see table below). Since there were no differences between control and treated groups, this change was not considered as treatment-related.

Total and percent frequency of ocular discomfort observed in rats

Group	Concentration (%)	N	Total # of observations	Severity					Duration				
				Non	1	2	3	4	Non	1	2	3	4
Males													
1	0	12	84	68	16	0	0	0	68	16	0	0	0
			100%	81	19	0	0	0	81	19	0	0	0
2	0.05%	12	84	62	19	3	0	0	62	22	0	0	0
			100%	74	23	4	0	0	74	26	0	0	0
3	0.1%	12	84	57	24	3	0	0	57	25	2	0	0
			100%	68	29	4	0	0	68	30	2	0	0
4	0.5%	12	84	64	19	1	0	0	64	18	2	0	0
			100%	76	23	1	0	0	76	21	2	0	0
Females													
1	0	12	84	39	43	2	0	0	39	35	9	1	0
			100%	46	51	2	0	0	46	42	11	1	0
2	0.05%	12	84	32	40	12	0	0	32	32	19	1	0
			100%	38	48	14	0	0	38	38	23	1	0
3	0.1%	12	84	37	38	9	0	0	37	39	8	0	0
			100%	44	45	11	0	0	44	46	10	0	0
4	0.5%	12	84	44	31	9	0	0	44	31	8	1	0
			100%	52	37	11	0	0	52	37	10	1	0

Severity: Non = No reaction, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe
Duration: Non = No reaction, 1 = 1 to 30 sec, 2 = 31to 60 sec, 3 = 61to 120 sec, 4 = 121 sec and more

Body weights: No treatment-related differences were noted.

Food consumption: No treatment-related differences were noted.

Clinical pathology: No biologically relevant effects of epinastine on clinical chemistry and hematology were observed.

Organ weights: There were no statistically significant differences in absolute and relative organ weights of adrenals, brain, gonads, heart, kidneys, liver, and spleen between control and treated animals. At the end of the treatment period, the thymus weights of HD animals were lower than those in the control group, although not statistically significant (see table below). The toxicological significance was not known. At the end of the recovery period, the thymus weights between control and HD animals were similar.

Thymic weights in rabbits treated with epinastine HCl ophthalmic solution (mean ± SD)

	Males				Females			
Group	1	2	3	4	1	2	3	4
Thymus								
6-month (g)	3.83±1.00	3.20±0.67	3.72±1.07	3.22±0.80	3.91±1.16	3.11±1.36	3.38±1.12	2.83±1.37
6-month (%)	0.115±0.035	0.095±0.019	0.110±0.032	0.095±0.023	0.102±0.029	0.084±0.037	0.092±0.028	0.078±0.031

Gross pathology: No treatment-related abnormalities were noted. Small thymus was noted in 2 (1 female), 7 (5 females), 6 (3 females) and 9 (6 females) rabbits in Groups 1, 2, 3 and 4, respectively. This finding was corresponding to the thymic atrophy in histopathologic examination. The sponsor indicated that this finding was likely due to involution and was not treatment-related. At the end of the recovery period, small thymus was only observed in one Group 1 female and two Group 3 females.

Microscopic examination: No treatment-related findings were noted. Minimal to mild spontaneous changes, including chronic atrophy of Harder's gland, hyperplasia of the sub-mucosal lymphoid nodules of the eyelids, and goblet cell hyperplasia of the conjunctival

epithelium, were noted in both eyes of treated and control groups. Thymic atrophy was noted in all groups, but predominated among the drug-treated groups (see table below). The sponsor indicated that this finding was likely due to involution and was not treatment-related.

Thymic atrophy in rabbits treated with epinastine HCl ophthalmic solution

	Males				Females			
Group	1	2	3	4	1	2	3	4
N	1	2	3	3	1	5	3	6
Thymus, atrophy								
Minimal	0	0	0	3	0	3	0	5
Mild	0	2	2	0	1	1	2	0
Moderate	0	0	1	0	0	0	1	1
Marked	0	0	0	0	0	1	0	0

PK/TK: Results are summarized in the table below. Epinastine was observed into the systemic circulation following ocular dosing. The exposure increased proportionally with increasing dose. No differences were noted between males and females.

Overall TK parameters in rabbits treated with epinastine HCl ophthalmic solution (mean ± SD)

	Treatment	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)
Day 26	0.05% epinastine HCl	0.79±0.46	0.5	1.13±0.12
	0.1% epinastine HCl	1.25±0.70	0.5	2.04±0.18
	0.5% epinastine HCl	5.17±3.78	0.5	7.79±0.85
Day 175	0.05% epinastine HCl	0.56±0.30	0.5	1.08±0.11
	0.1% epinastine HCl	1.00±0.49	0.5	1.70±0.14
	0.5% epinastine HCl	3.25±1.09	0.5	6.10±0.37

In summary, New Zealand white rabbits were topically treated with 0.05%, 0.1% or 0.5% epinastine HCl ophthalmic solution 3 times a day for 6 months. No drug-related effects on mortality, clinical signs, body weights, food consumption, ocular examinations, and clinical pathological examinations were noted. Postmortem examinations showed small thymus, decreased thymic weight, and thymic atrophy predominated among the drug-treated groups. The sponsor indicated that this finding was likely due to involution, and similar findings were not observed in other toxicity studies. Therefore, the thymic changes were not considered as treatment-related. No other toxicologically significant findings were noted. In conclusion, epinastine HCl ophthalmic solution (0.05% to 0.5%, tid x 6 months) did not elicit significant ocular or systemic toxicity.

TX00033: Epinastine: A six-month ocular toxicity study in monkeys. Vol. 18, Page 144

Key study findings: Ocular topical treatment with epinastine HCl ophthalmic solution (0.05%, 0.1% and 0.5%) to cynomolgus monkeys (tid x 6 months) was well tolerated. There were no drug-related ocular and systemic toxic effects.

Study #: TX00033
Study #: 0982-119
Study location: [redacted]

Study initiate date: 8/14/2000
Compliance with GLP/QAU: Yes

Study aim: To determine the ocular toxicity of epinastine HCl ophthalmic solution following tid topical ocular administration to cynomolgus monkeys for 6 months followed by a 1-month recovery period.
Compound/vehicle: 0.05%, 0.1%, and 0.5% epinastine HCl ophthalmic solution; the composition of drug and vehicle is listed in the following table, which was similar to the clinical formulation.

Ingredient (% w/v)	Vehicle Lot #: 11764	0.05% epinastine HCl Lot #: 11765	0.1% epinastine HCl Lot #: 11766	0.5% epinastine HCl Lot #: 11767
Formulation #	9342X	9343X	9347X	9346X
Epinastine HCl	0	0.05%	0.1%	0.5%
Benzalkonium chloride	0.01	0.01	0.01	0.01
Edetate disodium, USP				
Monobasic sodium phosphate				
Sodium chloride				
Purity				

Dose and route: One drop (35 μl)/eye, left eyes only, tid (at 3-hr intervals) for 6 months.
Animals: Cynomolgus monkeys, 2.3-3.6 years old, weighing 2.2-3.2 kg for males and 2.3-2.9 kg for females; 4/sex/group
Study Design: Epinastine HCl ophthalmic solution or vehicle was applied to the left eye (1 drop/35 μl/eye) of each monkey tid for 6 months as shown in the following table.

Group	Epinastine HCl	Number of Animals	Treatment Frequency	Dosing Duration (Days)
1	Vehicle	4/sex/group Main study: 3/sex; Recovery: 1/sex	tid	6 months
2	0.05%			
3	0.1%			
4	0.5%			

The day of the first dosing was designated as day 1. The following parameters were monitored.

Mortality and clinical observations: At least twice daily
Gross ocular observations: Weekly
Body weights: Weekly
Food consumption: Daily
Physical examination (including abdominal palpation, observations of the condition of integument, respiratory and cardiovascular systems): Days 87, 178 and 209
Ophthalmic evaluation (biomicroscopic examination, indirect ophthalmoscopic examination, and IOP examination): Days 80 and 167, and at the end of the recovery period
Clinical pathology: Pretreatment, days 90, 180, and 210
Necropsy: All animals
Organ weights: The following tissues and organs from all animals were weighted: adrenal glands, brain, epididymides, kidneys, liver, heart, ovaries, spleen, testes, thyroid with parathyroids, pituitary, and thymus.
Histopathology: The ocular tissues from all animals were observed histopathologically.
PK/TK: Days 28 and 174. Blood samples were collected from 4/sex animals in all groups prior to the 3rd daily dosing, and at 0.5, 1, 2, 3, 4, 6, and 8 hr post the last dose.

Results:

Mortality and clinical observations: No death occurred during the treatment period. No clinical signs attributed to topical ocular treatment with epinastine were noted.

Gross ocular observations: No ocular irritation (hyperemia, chemosis, and ocular discharge) was present in this study. There were no abnormal gross ocular observations in any of the animals.

Body weights: No treatment-related effects on body weights were noted.

Food consumption: No treatment-related differences were noted.

Physical examination: No treatment-related effects on physical examination were noted

Ophthalmic evaluation: No drug-related abnormal findings were observed. The only abnormal finding in the indirect ophthalmoscopic examination was a focal white opacity in the left retina with 2-3 foci of depigmentation adjacent to it in one Group 2 female at the 6-month examination. In the table submitted with this report, it was indicated that this finding occurred in the right eye (untreated eye). The lesion had resolved by the end of the recovery period. The sponsor indicated that this lesion might be associated with a transient focal retinitis that was incidental and unrelated to the treatment. The only abnormality at the biomicroscopic examination was a superficial linear scar on the left cornea of a control female. It was not drug-related. No treatment-related differences in IOP were noted between the control and treated groups.

Clinical pathology: No biologically relevant effects of epinastine on clinical chemistry, hematology, and coagulation measurements were observed.

Organ weights: There were no drug-related effects on absolute and relative organ weights between control and treated animals.

Gross pathology: No treatment-related abnormalities in ocular and systemic tissues were noted.

Microscopic examination: No treatment-related findings were noted. Lymphoplasmacytic inflammation, lymphoid nodules, and goblet cell hyperplasia in the eyelids were observed in all groups, and were considered incidental and unrelated to treatment with epinastine HCl.

Lymphoplasmacytic inflammation, lymphoid nodules, and goblet cell hyperplasia in the eyelids in monkeys treated with epinastine HCl ophthalmic solution

	Males				Females			
Group	1	2	3	4	1	2	3	4
N	3	3	3	3	3	3	3	3
Eyelid, upper, left								
Inflammation, lymphoplasmacytic, minimal	3	3	2	2	3	3	3	2
Hyperplasia, goblet cell, minimal	0	0	0	1	0	0	0	1
Lymphoid nodule, minimal	0	0	1	0	1	0	0	1
Lymphoid nodule, mild	1	0	0	0				
Eyelid, lower, left								
Inflammation, lymphoplasmacytic, minimal	3	3	3	2	1	3	3	3
Hyperplasia, goblet cell, minimal	0	1	0	2	0	0	1	1
Lymphoid nodule, minimal	0	1	0	0	1	2	2	1
Eyelid, upper, right								
Inflammation, lymphoplasmacytic, minimal	2	2	1	2	2	2	3	2
Hyperplasia, goblet cell, minimal	0	0	0	1	0	0	0	1
Lymphoid nodule, minimal	3	2	0	1	0	0	1	0
Eyelid, lower, right								
Inflammation, lymphoplasmacytic, minimal	3	3	2	2	3	2	3	2
Hyperplasia, goblet cell, minimal	0	1	0	0				
Lymphoid nodule, minimal	2	1	1	0	0	2	2	1

PK/TK: Results are summarized in the table below. Epinastine was observed into the systemic circulation following ocular dosing. The exposure increased proportionally with increasing dose. No significant differences were noted between males and females.

Overall TK parameters in monkeys treated with epinastine HCl ophthalmic solution (mean ± SD)

	Treatment	Cmax (ng/ml)	Tmax (hr)	AUC_{0-t} (ng-hr/ml)
Day 28	0.05% epinastine HCl	0.170±0.035	0.563±0.678	0.441±0.213
	0.1% epinastine HCl	0.325±0.106	0.313±0.458	1.00±0.51
	0.5% epinastine HCl	1.86±0.61	0.813±0.799	7.52±1.90
Day 174	0.05% epinastine HCl	0.148±0.091	1.00±0.89	0.486±0.345
	0.1% epinastine HCl	0.231±0.085	0.938±1.270	0.849±0.381
	0.5% epinastine HCl	1.51±0.70	0.813±0.530	6.06±2.30

In summary, cynomolgus monkeys were topically treated with 0.05%, 0.1% or 0.5% epinastine HCl ophthalmic solution 3 times a day for 6 months. No drug-related effects on mortality, clinical signs, body weights, food consumption, ocular examinations, clinical pathological examinations and post-mortem examinations were noted. In conclusion, ocular topical treatment with epinastine HCl ophthalmic solution (0.05%, 0.1% and 0.5%) to cynomolgus monkeys (tid x 6 months) was well tolerated. There were no drug-related ocular and systemic toxic effects.

U93-0709: 4-week local ocular tolerance study of WAL 801 CL eye drops by instillation into the conjunctival sac of rabbits. Vol. 35, Page 001

Key study findings: Ocular topical treatment with WAL 801 eye drops (0.1%, 0.3% and 0.5%) to rabbits (6 times/day x 4 weeks) induced no drug-related ocular and systemic toxicity.

Study №: U93-0709
Report #: 7612/92
Study location: [redacted]
Study initiate date: December 15, 1992

Compliance with GLP/QAU: Yes
Study aim: To determine the ocular toxicity of WAL 801 eye drops following 6 times/day topical ocular administration to rabbits (pigmented Himalayan) for 4 weeks followed by a 1-month recovery period.
Compound/vehicle: 0.1%, 0.3%, and 0.5% WAL 801 eye drops; the composition of drug and vehicle is listed in the following table. The drug was stable until March 1993.

Ingredient (% w/v)	Vehicle	0.1% WAL 801 eye drops	0.3% WAL 801 eye drops	0.5% WAL 801 eye drops
Batch #	F3046	F3047	F3048	F3049
WAL 801 CL	0	[redacted]		
Benzalkonium chloride	0.01	0.01	0.01	0.01
Edetate disodium, USP	[redacted]			

Dose and route: One drop (50 μl)/eye, right eyes only, 6 times/day (at 45-min intervals) for 4 weeks. The left eye remained untreated.
Animals: Rabbits/Himalayan (pigmented), 5 months old, weighing 2.0-2.7 kg for males and 1.9-2.6 kg for females, 5-6/sex/group
Study design: WAL 801 eye drops or vehicle was applied to the right eye (1 drop/50 μl/eye) of each rabbit 6 times/day for 4 weeks as shown in the following table.

Group	WAL 801 eye drops	Main study animals	Recovery animals	Dosing frequency	Dosing duration
1	Vehicle	6/sex	1/sex	6/day	4 weeks
2	0.1%	5/sex		6/day	
3	0.3%	5/sex		6/day	
4	0.5%	6/sex	1/sex	6/day	

The following parameters were monitored.

Clinical observations: 1x/day
Gross ocular observations: 2x/day
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopic, funduscopic, and fluorescein staining examinations: Pretreatment and weekly
Slit lamp biomicroscopic: Pretreatment and weekly
Hearing and dentition: At the ends of the treatment and recovery periods.
Necropsy: All animals
Organ weights: The following tissues and organs from all animals were weighted: adrenal glands, brain, kidneys, liver, lungs, heart, ovaries, pituitary, spleen, testes, thyroid, and thymus.
Histopathology: Both eyes and adnexa from all animals were examined histopathologically.
PK/TK: Day 28. Blood and aqueous humor samples were collected from 2/sex animals in all groups at 30 min post the last dose.

Results:

Mortality and clinical observations: No death occurred during the treatment period. No clinical signs attributed to topical ocular treatment with WAL 801 CL were noted.

Body weights: No treatment-related differences were noted.

Food consumption: No treatment-related differences were noted.

Gross ocular observations: No drug-related, biologically relevant changes were noted. A mild increased conjunctival secretion was seen once in one HD female and one HD male, and twice in two HD females in the treated eyes.

Ophthalmoscopic examinations: No toxicologically significant, treatment-related changes were noted.

Hearing and dentition: No treatment-related changes were noted.

Organ weights: There were no statistically significant differences in absolute and relative organ weights of adrenals, brain, gonads, heart, kidneys, liver, and spleen between control and treated animals.

Gross pathology: No treatment-related abnormalities were noted.

Microscopic examination: No treatment-related findings were noted.

PK/TK: Results were not included.

In summary, rabbits (pigmented Himalayan) were topically treated with 0.1%, 0.3% or 0.5% WAL 801 eye drops 6 times a day for 4 weeks. No drug-related effects on mortality, clinical signs, body weights, food consumption, ocular examinations, and postmortem examinations were noted. In conclusion, WAL 801 eye drops (0.1% to 0.5%, 6 times per day for 4 weeks) did not elicit significant ocular or systemic toxicity.

U97-2105: Epinastine (WAL 801 CL): 4-week local ocular tolerance study of WAL 801 CL eye drops by instillation into the conjunctival sac of rabbits. Concentrations in aqueous humor and plasma on day 28. Vol. 36, Page 108

Key study findings: The systemic exposure to the drug was low, while the topical exposure to the drug was high.

Study №: U97-2105
LPT Report #: BB2A13, A0001004
Study location: Department of Pharmacokinetics and Drug Metabolism, Boehringer Ingelheim KG, D55216 Ingelheim am Rhein, Germany
Compliance with GLP/QAU: Yes
Study aim: This report is TK part to Study U93-0709
Compound/vehicle: 0.1%, 0.3%, and 0.5% WAL 801 eye drops
Dose and route: One drop (50 μl)/eye, right eyes only, 6 times/day (at 45-min intervals) for 4 weeks. The left eye remained untreated.
Animals: Rabbits/Himalayan (pigmented), 5 months old, weighing 2.0-2.7 kg for males and 1.9-2.6 kg for females, 12/sex/group
Study design: WAL 801 eye drops or vehicle was applied to the right eye (1 drop/50 μl/eye) of each rabbit 6 times/day for 4 weeks as shown in the following table.

Group	WAL 801 eye drops	Main study animals	Recovery animals	Dosing frequency	Dosing duration
1	Vehicle	6/sex	1/sex	6/day	4 weeks
2	0.1%	5/sex		6/day	
3	0.3%	5/sex		6/day	
4	0.5%	6/sex	1/sex	6/day	

PK/TK: On day 28, blood and aqueous humor samples were collected from 2/sex animals in all groups at 30 min post the last dose.

Results:

Results are summarized in the table below. The systemic exposure to WAL801 CL was low, while the topical exposure to the drug in the treated eye was high. The drug concentrations in the aqueous humor from untreated eyes were below the limit of quantitation (1.0 ng/ml).

Geometric means of drug concentrations at 30 min after the last dosing on day 28 (ng/ml)

Group	Dose	Aqueous humor (right eye, treated)	Aqueous humor (left eye, untreated)	Plasma
2	0.1%	**69.4**	**BLQ**	**BLQ**
3	0.3%	**1125.2**	**BLQ**	**1.9**
4	0.5%	**1074.9**	**BLQ**	**3.2**

BLQ: Below the limit of quantitation (—ng/ml)

U93-0782: Acute eye irritation study with "stressed" WAL 801 CL eye drops (0.1%), containing 0.5% WAL 2003 by instillation into the conjunctival sac of rabbits. Vol. 35, Page 217

Key study findings: Ocular topical treatment with "stressed" WAL 801 eye drops (0.1%, containing 0.5% WAL 2003) to rabbits induced no ocular and systemic toxicity.

Study №: U93-0782
Report #: 8150/93
Study location:

Study initiate date: July 14, 1993
Compliance with GLP/QAU: Yes
Study aim: To determine the ocular irritation/corrosion effects of WAL 801 eye drops with 5% WAL 2003 following a single topical ocular administration to rabbits.
Compound/vehicle: 0.1% WAL 801 eye drops containing 0.5% WAL 2003 (Batch #: F4057). The composition of drug was not provided. The drug was stable for the duration of the study.

Dose and route: One hundred μl/eye, left eyes only, single dose. The right eye remained untreated.
Animals: Rabbits/Himalayan (pigmented), males only, 4-6 months old, weighing 2.0-2.4 kg
Study design: WAL 801 eye drops was applied to the left eye (100 μl/eye) of 6 rabbit. No vehicle control group was included in this study.

The following parameters were monitored.

Clinical observations: Daily

Body weights: At the beginning and end of the study
Food consumption: Daily
Ophthalmoscopic examination with slit lamp biomicroscope: Prior to the treatment and at 5, 15, 30 min, and 1, 2, 4, 24, 48, and 72 hr after dosing
Fluorescein examination: At 24 hr after dosing

Results:

Mortality and clinical observations: No death occurred during the treatment period. No clinical signs attributed to topical ocular treatment were noted.

Body weights: No impairment was noted.

Food consumption: No impairment was noted.

Ocular observations: No drug-related, biologically relevant changes were noted in the cornea, iris, and conjunctiva of the rabbits included in the study.

Fluorescein test: No pathological changes were observed.

In summary, rabbits (Himalayan) were topically treated with a single dose of 0.1% WAL 801 eye drops containing 0.5% WAL 2003. There were no drug-related effects on mortality, clinical signs, body weights, food consumption, and ocular examinations. In conclusion, "stressed" WAL 801 eye drops (0.1%, containing 0.5% WAL 2003) did not elicit any ocular or systemic toxicity.

U95-0510: 13-week local ocular tolerance study with WAL 801 CL eye drops by instillation into the conjunctiva sac of rabbits. Vol. 35, Page 360

Key study findings: WAL 801 CL eye drops was weakly irritative at concentrations of 0.3% and higher.

Document №: U95-0510
Study #: E9409
Study location: Nippon Boehringer Ingelheim Co., Ltd., Kawanishi, Japan
Study initiate date: Not indicated.
Compliance with GLP/QAU: Yes
Study aim: To determine the ocular toxicity of epinastine HCl ophthalmic solution following tid topical ocular administration to New Zealand white rabbits for 3 months followed by a 1-month recovery period (HD animals only).
Compound/vehicle: 0.1%, 0.3%, and 0.5% epinastine HCl ophthalmic solution; the composition of drug and vehicle is listed in the following table, which was similar to the clinical formulation.

Ingredient (% w/v)	Vehicle	0.1% epinastine HCl	0.3% epinastine HCl	0.5% epinastine HCl
Batch #	F4144	F4145	F4146	F3049
Epinastine HCl	0	0.1	0.3	0.5
Benzalkonium chloride	0.01	0.01	0.01	0.01
Edetate disodium, USP				
Monobasic sodium phosphate				
Sodium chloride				

Dose and route: One drop (50 μl)/eye, right eyes only, tid (at 2-hr intervals) for 3 months. The left eye remained untreated.
Animals: male New Zealand white rabbits, 11-12 weeks old, weighing 2.1-2.6 kg, 5/group
Study design: Epinastine HCl ophthalmic solution or vehicle was applied to the right eye (50 μl/eye) of each rabbit tid for 3 months as shown in the following table.

Group	Epinastine HCl	Number of Animals	Treatment Frequency	Dosing Duration
1	PSS	5	tid	3 months
2	Vehicle	5		
3	0.05%	5		
4	0.1%	5		
5	0.5%	8 (3 recovery animals)		

The following parameters were monitored.

Clinical observations: 2x/day during the treatment period, and 1x/day during the recovery period
Body weights: Weekly
Food consumption: Weekly
Gross ocular observations: 2x/day (before the first and 1 hr after the third instillation)
Biomicroscopic examination: Pretreatment, Weeks 13 and 17
Fundus examination: Pretreatment, Weeks 13 and 17
Necropsy: Both eyes from all animals
Histopathology: Eye balls with the optic nerve, eyelids, lacrimal and Harderian glands

Results:

Mortality and clinical observations: No death occurred during the treatment period. No clinical signs attributed to topical ocular treatment with epinastine were noted.

Body weights: No treatment-related differences were noted.

Food consumption: No treatment-related differences were noted.

Gross ocular observations: No treatment-related abnormal findings were noted in the examinations conducted before the first instillation. At 1 hr after the instillation, conjunctival redness and discharge were observed in all treated groups in a dose-dependent manner. Positive findings were also noted in vehicle control group, suggesting the vehicle might contain the irritative agents. All HD animals showed conjunctival redness from Week 1 or 2. No abnormalities were noted in cornea and iris.

Weekly irritation score of conjunctiva after the 3rd instillation in rabbit eyes

	Saline			Vehicle			0.1% WAL 801 CL			0.3% WAL 801 CL			0.5% WAL 801 CL		
N	5			5			5			5			8		
WK	R	D	T	R	D	T	R	D	T	R	D	T	R	D	T
1	0	0	0	0	0	0	0	0	0	0	0	0	0.5	1.8	4.5
2	0	0	0	0	0	0	0	0.4	0.8	0	0.8	1.6	0.5	1.0	3.0
3	0	0	0	0	0.2	0.4	0	0.2	0.4	0	0	0	0.8	1.0	3.5
4	0	0	0	0	0.2	0.4	0.2	0	0.4	0	0	0	0.8	0.8	3.0
5	0	0	0	0	1.0	2.0	0	1.2	2.4	0	0.6	1.2	0	1.1	2.3
6	0	0	0	0	0.2	0.4	0.2	0.6	1.6	0.4	0.6	2.0	0.4	2.0	4.8
7	0	0	0	0	1.0	2.0	0	1.2	2.4	0	0.2	0.4	0.4	1.5	3.8
8	0.2	0.2	0.8	0	1.6	3.2	0.6	2.4	6.0	0.4	1.8	4.4	1.4	2.9	8.5
9	0	0	0	0	0.8	1.6	0.6	1.8	4.8	0	1.6	3.2	1.1	2.6	7.5
10	0	0	0	0.2	1.0	2.4	0.2	2.0	4.4	0.2	1.0	2.4	1.0	3.0	8.0
11	0	0	0	0	0.6	1.2	0	2.0	4.0	0	1.0	2.0	0.8	2.9	7.3
12	0	0	0	0	1.8	3.6	0	1.6	3.2	0	1.2	2.4	0.4	2.5	5.8
13	0	0	0	0	0.6	1.2	0	1.6	3.2	0	1.0	2.0	0	2.6	5.3

R: Redness, D: discharge, T: total score

The mean irritation score and grade classification are summarized in the table below. At the highest concentration (0.5%), WAL 801 CL eye drops were classified as practically non-irritating.

Mean irritation score and grade classification of WAL 801 CL eye drops in rabbits

Total irritation score / animal / day

Test Article	Number of Animals	Mean Irritation Score after the 3rd instillation												
week	1	2	3	4	5	6	7	8	9	10	11	12	13
saline	5	0.0(A)	0.0(A)	0.0(A)	0.0(A)	0.0(A)	0.0(A)	0.0(A)	0.1(A)	0.0(A)	0.0(A)	0.0(A)	0.0(A)	0.0(A)
vehicle	5	0.0(A)	0.0(A)	0.1(A)	0.1(A)	0.3(A)	0.1(A)	0.3(A)	0.5(A)	0.2(A)	0.3(A)	0.2(A)	0.5(A)	0.2(A)
0.1%WAL 801 CL	5	0.0(A)	0.1(A)	0.1(A)	0.1(A)	0.3(A)	0.2(A)	0.3(A)	0.9(B)	0.7(B)	0.6(B)	0.6(B)	0.5(A)	0.5(A)
0.3%WAL 801 CL	5	0.0(A)	0.2(A)	0.0(A)	0.0(A)	0.2(A)	0.3(A)	0.1(A)	0.6(B)	0.5(A)	0.3(A)	0.3(A)	0.3(A)	0.3(A)
0.5%WAL 801 CL	8	0.6(B)	0.4(A)	0.5(A)	0.4(A)	0.3(A)	0.7(B)	0.5(A)	1.2(B)	1.1(B)	1.1(B)	1.0(B)	0.8(B)	0.8(B)

( ): Classification of WAL 801 CL based on eye irritation properties

$0.0 \leq A \leq 0.5$: Non-Irritating

$0.5 < B \leq 2.5$: Practically Non-Irritating

Microscopic examination: Positive findings are summarized in the table below. A decrease in the number and size of the goblet cells in the epithelium of the lower palpebral conjunctiva near fornix was seen in vehicle and drug-treated groups. Hyperplasia of conjunctival epithelium was seen in MD and HD animals. These changes were reversible after 4-week recovery period in 3 HD animals. Other changes, including follicular hyperplasia of lymphatic tissues, infiltration of lymphoid cells in the lower palpebral conjunctiva, dilatation of lumen of Harderian glands with atrophy of epithelium, and infiltration of lymphoid cells in Harderian and lacrimal glands, were also seen in the untreated left eyes, and were not considered as treatment-related.

Positive histopathologic findings in rabbits treated with WAL 801 CL eye drops

		Saline	Vehicle	0.1% WAL 801 CL	0.3% WAL 801 CL	0.5% WAL 801 CL	Recovery
N		5	5	5	5	5	3
Lower lid	**Degree**						
Increase in basal cells	Very slight		2	2			1
	Slight		2	1	1		
Decrease in goblet cells	Very slight		1	1		1	
	Slight		4	3	3	2	
	Moderate				1	2	
Hyperplasia of conjunctival epithelium	Very slight				2	1	
	Slight				1	3	
	Moderate					1	
Infiltration of lymphocytes	Very slight				1		
	Slight				2	2	1
Harderian gland							
Dilatation of lumen	Slight				2	1	
	Moderate					1	
Infiltration of lymphocytes or plasma cells	Very slight	3	1	1	1	1	
	Slight					1	
Lacrimal gland							
Infiltration of lymphocytes or plasma cells	Very slight					2	
	Slight						1

In summary, New Zealand white rabbits were topically treated with 0.1%, 0.3%, or 0.5% epinastine HCl ophthalmic solution 3 times a day for 3 months. No drug-related effects on mortality, clinical signs, body weights, and food consumption were noted. Ocular examination showed conjunctival redness and discharge in vehicle and treated groups at 1 hr after the 3rd instillation in a dose-dependent manner. No treatment-related abnormal findings were noted in the ocular examinations conducted before the first instillation. Histopathologic examination showed hyperplasia with a decrease in the number and size of the goblet cells in the epithelium of the lower palpebral conjunctiva in MD and HD animals. These changes were recovered after 4-week recovery period. In conclusion, WAL 801 CL eye drops was weakly irritative at concentrations of 0.3% and higher.

U96-0105: 4-week local ocular tolerance study with WAL 801 CL eye drops by instillation into the conjunctiva sac of rabbits. Vol. 36, Page 001

Key study findings: WAL 801 CL eye drops was weakly irritative at concentrations of 0.5% and higher. The dose of 0.3% epinastine HCl ophthalmic solution qid was considered as the NOAEL in this study.

Document №: U96-0105
Study #: E9313
Study location: Nippon Boehringer Ingelheim Co., Ltd., Kawanishi, Japan
Study initiate date: Not indicated.
Compliance with GLP/QAU: Yes
Study aim: To determine the ocular toxicity of epinastine HCl ophthalmic solution following qid topical ocular administration to New Zealand white rabbits for 4 weeks
Compound/vehicle: 0.3%, 0.5%, and 1.0% epinastine HCl ophthalmic solution; the composition of drug and vehicle is listed in the following table, which was similar to the clinical formulation.

Ingredient (% w/v)	Vehicle	0.3% epinastine HCl	0.5% epinastine HCl	1.0% epinastine HCl
Batch #	F3046	F3048	F3049	93039
Epinastine HCl	0	0.3	0.5	1.0
Benzalkonium chloride	0.01	0.01	0.01	0.01
Edetate disodium, USP				
Monobasic sodium phosphate				
Sodium chloride				
NaOH				
Distilled water				

Dose and route: One drop (50 μl)/eye, right eyes only, qid (at 2-hr intervals) for 4 weeks. The left eye remained untreated.
Animals: Male New Zealand white rabbits, 3-month old, weighing 2.6-3.2 kg, 5/group
Study design: Epinastine HCl ophthalmic solution or vehicle was applied to the right eye (50 μl/eye) of each rabbit qid for 4 weeks as shown in the following table.

Group	Epinastine HCl	Number of Animals	Treatment Frequency	Dosing Duration
1	Physiological saline solution	5	qid (at 2-hr intervals)	4 weeks
2	Vehicle	5		
3	0.3%	5		
4	0.5%	5		
5	1.0%	5		

The following parameters were monitored.

Clinical observations: 2x/day
Body weights: Twice weekly
Food and water consumption: Weekly
Gross ocular observations and slit lamp biomicroscopic examination: 2x/week (before the 1st and 1 hr after the 4th instillation)
Biomicroscopic examination with fluorescein: At 1 hr after the last instillation on day 28
Fundus examination: Pretreatment, Weeks 2 and 4
Histopathology: Eye balls with the optic nerve, eyelids, lacrimal and Harderian glands
EM: Epithelium and endothelium of cornea and conjunctiva of 2 animals/group were examined by scanning electron microscopy. Cornea and conjunctiva of one PSS animal and two HD animals were examined by transmission electron microscopy.

Results:

Mortality and clinical observations: No death occurred during the treatment period. No clinical signs attributed to topical ocular treatment with epinastine were noted.

Body weights: No treatment-related differences in body weights were noted.

Food and water consumption: No treatment-related differences were noted.

Ocular observations: The average irritation scores are summarized in the table below. No abnormal findings were noted in the iris and cornea. No abnormal findings were seen in Group 1 animals (PSS). In vehicle control group, 2 animals showed lacrimation or eye mucus only in 1-2 days sporadically. In LD group, two animals showed lacrimation, eye mucus or conjunctival

redness only in 1-3 days sporadically. In MD and HD groups, all animals showed lacrimation, eye mucus or conjunctival redness. The irritative intensity did not worsen in the course of the 4-week treatment period. Three HD animals had these findings almost every day. The positive findings in the conjunctival tissues were only seen at 1 hr after the 4th instillation and disappeared in the next morning. Based on the score in the following table, animals in Groups 1 to 4 were evaluated as non-irritating (score range: 0-0.5), while HD animals were classified as practically non-irritating (score range: 0.5-2.5).

Average irritation score after the 4th instillation in rabbit eyes

Group	Treatment	N	Day 2	Day 6	Day 9	Day 13	Day 16	Day 20	Day 23	Day 27
1	PSS	5	0	0	0	0	0	0	0	0
2	Vehicle	5	0	0	0	0	0	0.4	0	0
3	0.3%	5	0	0	0	0	0.8	0	0	0
4	0.5%	5	0	0.4	0.4	0	0	0.4	0	0.4
5	1.0%	5	1.6	0.8	1.6	2.0	1.6	0.8	2.0	2.0

Microscopic Examination: Positive findings are summarized in the table below. The 4-5 layered hyperplasia of the basal cells and decrease of the goblet cells at the basement of the epithelium of the lower palpebral conjunctiva were noted in MD and HD animals. Slight hyperplasia in upper palpebral conjunctiva and in the 3rd lid, and discrete squamous cell metaplasia in the epithelium of lower palpebral conjunctiva were also seen in HD animals. Other findings were also seen in the untreated left eyes and were not considered as treatment-related.

Positive histopathologic findings in rabbits treated with WAL 801 CL eye drops

		Saline	Vehicle	0.3% WAL 801 CL	0.5% WAL 801 CL	1.0% WAL 801 CL
N		5	5	5	5	5
Lower lid	Degree					
Decrease in goblet cells	Slight				2	1
	Moderate					4
Simple hyperplasia of epithelium	Very slight				1	1
	Slight				1	4
Squamous metaplasia of epithelium	Slight					2
Upper lid						
Simple hyperplasia of epithelium	Very slight					2
Infiltration of lymphocytes or granulocytes	Very slight			1	1	1
Third lid						
Simple hyperplasia of epithelium	Very slight					1
Limbus						
Follicular hyperplasia of lymphoid tissue	Very slight				1	1

Transmission EM: No drug-related changes were noted.

Scanning EM: No data were provided.

In summary, New Zealand white rabbits were topically treated with 0.3%, 0.5%, or 1.0% epinastine HCl ophthalmic solution 4 times a day for 4 weeks. No drug-related effects on mortality, clinical signs, body weights, and food consumption were noted. Ocular examination showed conjunctival redness, eye mucus, and discharge in vehicle and treated groups at 1 hr after the 3rd instillation in a dose-dependent manner. No treatment-related abnormal findings were noted in the ocular examinations conducted before the first instillation in the morning.

Histopathologic examination showed hyperplasia in the epithelium of the upper or lower palpebral conjunctiva in MD and HD animals. A decrease in the number of goblet cells and a discrete squamous cell metaplasia in the epithelium of lower palpebral conjunctiva were also seen in HD animals. In conclusion, WAL 801 CL eye drops was weakly irritative at the concentrations of 0.5% and higher. The dose of 0.3% epinastine HCl ophthalmic solution qid was considered as the NOAEL in this study.

Summary and conclusion of ocular toxicity studies:

Several ocular toxicity studies with duration ranging from 1 month to 6 months were conducted in Himalayan rabbits, New Zealand white (NZW) rabbits, and cynomolgus monkeys.

In the 1-month study conducted in Himalayan rabbits, WAL 801 eye drops (0.1% to 0.5%, 6 times per day for 4 weeks) did not elicit drug-related ocular or systemic toxicity.

In the 1-month (qid treatment) and 3-month (tid treatment) studies conducted in NZW rabbits, weak irritant responses evidenced by transient hyperemia and conjunctival discharge were observed after the last daily instillation at concentrations ≥ 0.3% and 0.5% in the 3-month and 1-month studies, respectively. These signs disappeared by the next morning. The irritancy potential was classified as practically non-irritating at the highest concentrations used in these two studies. Histopathological examination showed reduced number and size of epithelial goblet cells and epithelial hyperplasia of the palpebral conjunctiva in drug-treated rabbits. The severity of these changes increased with increasing concentration. A slight decrease in the number and size of epithelial goblet cells was also seen in vehicle control animals in the 3-month study. All conjunctival changes were reversible following a 4-week recovery period.

In two 6-month ocular toxicity studies conducted in NZW rabbits and cynomolgus monkeys, animals were treated at concentrations of 0.05%, 0.1% or 0.5% epinastine, one drop in the left eye (tid). The drug was well tolerated. No toxicologically significant abnormalities were noted. At the highest concentration, 0.5% epinastine, daily AUC exposure in the rabbit and monkey was 8.7-fold human exposure (one drop of 0.05% epinastine in both eyes, bid).

Systemic exposure to epinastine HCl in rabbits and monkeys after 6-month ocular treatment

	Treatment	Dosing frequency	Cmax (ng/ml)	Animal/human	AUC (ng-hr/ml)	Animal/human
Human	0.05%	bid	0.042		0.7	
Rabbit	0.5%	tid	3.25	77	6.1	8.7
Monkey	0.5%	tid	1.51	36	6.1	8.7

The sponsor indicated that positive ocular observations in the 1- and 3-month studies might be artifactual. "The most likely explanation was that rabbit eyes were irritated during the ocular treatment itself, e.g., by the method used to open the conjunctival sac, or perhaps the irritation was caused by a substance in the investigators' gloves. An anomaly based on animal handling would account for the conjunctival hyperemia and discharge, and subsequent histopathological findings, observed in control and drug-treated rabbits." Considering that the weak irritating results from the 1- and 3-month studies were transient, reversible, and not seen in other studies, the reviewer believes that positive observations do not present great safety concerns for the clinical application of the drug product. In conclusion, epinastine HCl eye drops were weakly irritating to rabbit eyes in two studies. In the other ocular toxicity studies in rabbits

and monkeys, the drug was well tolerated. Based on nonclinical data, epinastine HCl ophthalmic solution presented no safety concerns regarding its clinical application.

Other studies:

U88-0583: WAL 801 CL: Skin sensitization study in guinea pigs (Guinea pig maximization test). Vol. 25, Page 403
U94-0093: Examination of WAL 801 CL eye drops 0.5% in a skin sensitization test in guinea pigs according to Magnusson and Kligman (maximization test). Vol. 35, Page 239
U94-0228: Skin sensitization study of epinastine hydrochloride (WAL 801 CL) eye drops in guinea pigs—supplement study by Buelher Test. Vol. 35, Page 276
U94-0290: Skin sensitization study of epinastine hydrochloride (WAL 801 CL) eye drops in guinea pigs. Vol. 35, Page 318
U97-2455: Photosensitization test of WAL 801 CL eye drops 0.05% by dermal administration to guinea pigs. Vol. 36, Page 141
U97-2456: Phototoxicity study of WAL 801 CL eye drops 0.05% by dermal administration to guinea pigs. Vol. 36, Page 187

U88-0583: WAL 801 CL: Skin sensitization study in guinea pigs (Guinea pig maximization test). Vol. 25, Page 403

Key study findings: WAL 801 CL revealed no sensitizing potential under the present study conditions.

Document #: U88-0583
Study Nº: 63/87
Conducting laboratory and location: Research Division, Department of Experimental Pathology and Toxicology, Boehringer Ingelheim Pharma KG, D-6507 Ingelheim am Rhein
Date of study initiation: October 12, 1987
GLP compliance: Yes
QA report: Yes
Drug: WAL 801 CL, Batch #: XI (2.5% WAL 801 CL solution in distilled water for intradermal injection, and 25% WAL 801 CL suspension in absolute ethanol for occlusive application)
Animal: Female guinea pigs/Pirbright white, 9-10 weeks old, 460.9 ±30.3 g, 10/group

The purpose of this study was to evaluate the allergenic potential of WAL 801 CL in guinea pigs. The experiment procedure is as follows. [**Reviewer's comments**: No positive control groups were included.]

	Sensitization phase		Challenge phase	
Group	1st day of study	8th day of study	22nd day of study, dermal application	
	3 pairs of intradermal injections, dorsal skin	Dermal application	Left flank	Right flank
1	0.1 ml of distilled water	48 hr occlusive 0.4 ml absolute ethanol	24 hr occlusive 0.2 ml	24 hr occlusive 0.2 ml absolute ethanol
	0.1 ml of a 1:1 mixture of FCA and 0.9% NaCl solution			
	0.1 ml of a 1:1 mixture of FCA and distilled water			
2	0.1 ml of 25% WAL 801 CL solution in distilled water	48 hr occlusive 0.4 ml of 25% WAL 801 CL suspension in absolute ethanol	25% WAL 801 CL suspension in absolute ethanol	
	0.1 ml of a 1:1 mixture of FCA and 0.9% NaCl solution			
	0.1 ml of a 1:1 mixture of FCA and 25% WAL 801 CL solution in distilled water			

Twenty-four and 28 hr after removal of occlusive dressings, the areas of application were evaluated based on the following point system:

0: No reaction, 1: Slight reddening (points or spots), 2. Moderate reddening of the whole area of application, 3. Severe reddening and swelling
Body weights were measured weekly.

Results:

One Group 2 animal (pretreated) showed slight reddening (score = 1) on the left flank at 24 hr after removal of occlusive dressings. No positive findings were noted at 48 hr after removal of occlusive dressings.

No drug-related body weight changes were noted.

In conclusion: WAL 801 CL did not possess skin sensitizing potential in guinea pigs.

U94-0093: Examination of WAL 801 CL eye drops 0.5% in a skin sensitization test in guinea pigs according to Magnusson and Kligman (maximization test). Vol. 35, Page 239

Key study findings: WAL 801 CL revealed no sensitizing potential under the present study conditions.

Document #: U94-0093
Study Nº: 8374/93, A0001106
Conducting laboratory and location: [redacted]
Date of study initiation: September 21, 1993
GLP compliance: Yes
QA report: Yes
Drug: WAL 801 CL eye drops 0.5%, Batch #: F3409. The drug was stable until March 30, 1994.
Animal: Male guinea pigs/Pirbright white, 36 days old, 229-375 g, 10/group
(+) Control: Penicillin-g-sodium/potassium, 4500 iu for intracutaneous injection and 400000 iu for topical application [**Reviewer's comments**: Positive control data were from a historical control group. There was no concurrent positive control group in this study.]

The purpose of this study was to evaluate the effects of WAL 801 CL eye drops 0.5% on a skin sensitization test in guinea pigs. The experiment procedure is as follows.

	Sensitization phase		Challenge phase	
Group	Day 0 of study	Day 7 of study	Day 22 of study, dermal application	
	3 pairs of intradermal injections, dorsal skin	Dermal application	Left flank	Right flank
1	0.1 ml Freund's adjuvant (diluted 1:1 with 0.9% NaCl solution)	48 hr occlusive 2 ml test compound placebo	24 hr occlusive 2 ml	24 hr occlusive 2 ml
	0.1 ml of test compound placebo			
	0.1 ml of a 1:1 mixture of FCA and test compound placebo			
2	0.1 ml Freund's adjuvant (diluted 1:1 with 0.9% NaCl solution)	48 hr occlusive 2 ml test compound	0.5% WAL 801 CL eye drops	0.5% WAL 801 CL eye drops (placebo)
	0.1 ml of test compound (WAL 801 CL eye drops 0.5%)			
	0.1 ml of a 1:1 mixture of FCA and test compound			

Twenty-four, 48 and 72 hr after removal of occlusive dressings, the areas of application were evaluated based on the following point system:

Erythema and eschar formation		Edema formation		Maximization grading		
	Value		Value	Grade	Sensitization rate (%)	Classification
No erythema	0	No edema	0	0	0	No indication of sensitizing properties
Very slight erythema	1	Very slight edema	1	I	1-8	Weak
Well-defined erythema	2	Slight edema	2	II	9-28	Mild
Moderate to severe erythema	3	Moderate edema	3	III	29-64	Moderate
Severe erythema to slight eschar formation	4	Severe edema	4	IV	65-80	Strong
				V	81-100	extreme

Results:

Under the present test condition, WAL 801 CL eye drops 0.5% revealed no sensitizing properties in guinea pigs. A score of zero was achieved in all drug- and placebo-treated groups.

No drug-related abnormalities in clinical observations and body weights were noted.

In conclusion: WAL 801 CL did not possess skin sensitizing potential in guinea pigs in this study.

U94-0290: Skin sensitization study of epinastine hydrochloride (WAL 801 CL) eye drops in guinea pigs. Vol. 35, Page 318

Key study findings: WAL 801 CL had skin sensitizing potential under the present study conditions.

Document #: U94-0290
Study Nº: 8123
Conducting laboratory and location: [redacted]
Date of study initiation: July 23, 1993
GLP compliance: Yes
QA report: Yes
Drug: 0.5%, 1%, and 5% Epinastine HCl (WAL 801 CL) eye drops, Lot #s: F3049, 93039, 93041
WAL 801 CL: Lot #: XII
Positive control: 2,4-dinitrochlorobenzene (DNCB)
Animal: Male guinea pigs/Crj:Hartley, 4 weeks old, 264-301 g, 5/group

The purpose of this study was to evaluate the allergenic potential of WAL 801 CL eye drops in guinea pigs. The experiment procedure is as follows.

	Sensitization phase		Challenge phase	
Group	1st day of study	8th day of study	22nd day of study, dermal application	
	3 pairs of intradermal injections, 0.05 ml/site, dorsal skin	Dermal application	Left flank	Right flank
1	Non-treated	Non-treated	24 hr occlusive 100 mg of 0.01% DNCB ointment	24 hr occlusive 100 mg 25% WAL 801 CL in white vaseline and 10% ointment of sodium lauryl sulfate
2	Saline + FCA	48 hr occlusive 200 mg of 25% WAL 801 CL in white vaseline and 10% ointment of sodium lauryl sulfate		
0.5% WAL CL eye drops	0.5% WAL CL eye drops			
	0.5% WAL CL eye drop + FCA			
3	Saline + FCA			
1% WAL CL eye drops	1% WAL CL eye drops			
	1% WAL CL eye drop + FCA			
4	Saline + FCA			
5% WAL CL eye drops	5% WAL CL eye drops			
	5% WAL CL eye drop + FCA			
5	Saline + FCA	48 hr occlusive 200 mg of 1% DNCB ointment		24 hr occlusive 100 mg of 0.01% DNCB ointment
DNCB	DNCB (0.1% corn oil solution)			
	DNCB (0.4% corn oil solution) + FCA + saline			

Twenty-four, 48 and 72 hr after the initiation of occlusive dressings, the areas of application were evaluated based on the following point system:

0: No reaction, 1: scattered mild redness, 2. Moderate and diffuse redness, 3. Intense redness and swelling
Clinical observations were performed daily.
Body weights were measured weekly.

Results:

One preliminary test was conducted in 3 guinea pigs. Three sites on the back of each animal were treated with test ointments (5%, 10% and 25% WAL 801 CL ointments) by closed-patch exposure for 24 hr. Skin reactions (erythema and edema) were evaluated at 24, 48 and 72 hr after the initiation of closed-patch exposure. No skin reactions were observed in all ranges of concentrations examined.

In the main study, no abnormal clinical observations were noted. In the drug-treated groups, body weights and body weight gain were lower than those in untreated animals (see table below).

Body weight changes in guinea pigs (g, mean ± SD)

Group	Day 0	Day 25	% control	Body weight gain (day 0-day 25)	% control
1	332±8.6	536±18.9	100	204	100
2	327±10.2	485±16.9	90.5	158	77.5
3	326±8.3	485±43.5	90.5	159	77.9
4	327±6.7	490±22.5	91.4	163	79.9
5	331±13.0	484±35.6	90.3	153	75

In the non-treated group, neither challenge by WAL 801 CL nor by DNCB caused any skin reactions in any of the animals at any time points. However, in WAL 801 CL treated groups, similar to positive control group, at 24 hr after challenge, intense redness and swelling (score 3) were noted in all animals except for one low dose animal with a score of "1". At 48 hr and 72 hr time points, scattered mild redness and moderate and diffuse redness (score 2 or 1) were noted in all treated animals. Significant differences in the degrees of skin reactions were

observed between non-treated animals and each of the treated groups at each time point. WAL 801 CL eye drops had skin sensitization potential in this study.
[**Reviewer's comments**: The sponsor indicated that the positive response observed in this test was attributed to experimental design rather than a drug-related effect. Several explanations were provided by the sponsor.

1. The animals of the negative control group were not treated during the induction phase. In a regular Guinea Pig Maximization Test (GPMT) according to Magnusson and Kligman, however, the animals of the control group should be treated during sensitization phase as the animals of the test group, but with vehicle only.
2. On day 7 the animals of the test groups were treated with 10% sodium laurilsulfate ointment in vaseline. Again, the animals of the control group were not treated.
3. The animals of the test groups were treated with ointments in vaseline not only during the sensitization phase, but also at the challenge time point, but there was no control group treated with vaseline during these time points. Thus, it could be excluded that the reactions seen after the challenge were elicited by the treatment with vaseline or a combination of vaseline plus test substance.
4. The first evaluation of the skin reactions (24 hr) was performed a few minutes after removal of the occlusive bandage and not 24 hr after removal of the occlusive patches, as recommended by the GPMT. The reactions recorded at this time could not be considered as allergic reactions because they were the result of the occlusive treatment.

The reviewer agrees with the sponsor on the first 3 explanations. For the last explanation, positive response was also noted in the 2nd and 3rd time points. In conclusion, several deficiencies were noted in study design. The study was not valid.

U94-0228: Skin sensitization study of epinastine hydrochloride (WAL 801 CL) eye drops in guinea pigs—supplement study by Buelher Test. Vol. 35, Page 276

Key study findings: WAL 801 CL showed no skin sensitizing potential under the present study conditions.

Document #: U94-0228
Study Nº: 8193
Conducting laboratory and location: [redacted]
Date of study initiation: October 4, 1993
GLP compliance: Yes
QA report: Yes
Drug: 0.5%, 1%, and 5% Epinastine HCl (WAL 801 CL) eye drops, Lot #S: 93064, 93039, 93041
Relative control: Zaditen (ketotifen fumarate eye drops), Lot #: P256H
Positive control: 2,4-dinitrochlorobenzene (DNCB)
Animal: Male guinea pigs/Crj:Hartley, 4 weeks old, 236-287 g, 5/group

The purpose of this study was to evaluate the allergenic potential of WAL 801 CL eye drops in guinea pigs. The study was performed because positive results were observed in Study U94-0290. The experiment procedure is as follows.

	Sensitization phase	Challenge phase
Group	**24-hr closed patch exposure, on a shaven area 2 cm x 4 cm covering the median line, every other day, three times a week for 3 weeks**	**Two weeks after the final sensitization application, 24-hr closed patch exposure, on a shaven area 2 cm x 4 cm covering the median line**
1	Non-treated	0.5%, 1%, and 5% WAL 801 CL eye drops, Zaditen, and 0.1% DNCB ointment
2	0.5% WAL 801 CL eye drops, 0.25 ml	0.5% WAL 801 CL eye drops, 0.1 ml
3	1% WAL 801 CL eye drops, 0.25 ml	1% WAL 801 CL eye drops, 0.1 ml
4	5% WAL 801 CL eye drops, 0.25 ml	5% WAL 801 CL eye drops, 0.1 ml
5	Zaditen, 0.25 ml	Zaditen, 0.1 ml
6	0.1% DNCB ointment, 250 mg	0.1% DNCB ointment, 100 mg

Twenty-four, 48 and 72 hr after the initiation of occlusive dressings, the areas of application were evaluated based on the following point system:

Erythema and eschar formation		Edema formation	
	Value		Value
No erythema	0	No edema	0
Very slight erythema	1	Very slight edema	1
Well-defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

Clinical observations were performed daily.
Body weights were measured on days 0, 7, 14, 18, 25, 32 and 35.

Results:

No abnormal clinical observations and body weight changes were noted.

In the non-treated group, neither challenge by WAL 801 CL and Zaditen nor by DNCB caused any skin reactions in any of the animals at any time points. In WAL 801 CL and Zaditen treated groups, no skin reactions were noted in any animals at any time of observation. The scores of "0" were noted in all of the animals. On the other hand, DNCB caused clear positive responses. In conclusion, WAL 801 CL eye drops did not present skin sensitizing potential under the present study conditions.

U97-2455: Photosensitization test of WAL 801 CL eye drops 0.05% by dermal administration to guinea pigs. Vol. 36, Page 141

Key study findings: WAL 801 CL did not possess photosensitizing potential in guinea pigs in this study.

Document #: U97-2455
Study Nº: 10277/1/97, A0001108
Conducting laboratory and location: [redacted]

Date of study initiation: April 14, 1997
GLP compliance: Yes
QA report: Yes

Drug: WAL 801 CL eye drops 0.05%, Batch #: 603055. The drug was stable until September 30, 1997.
WAL 801 CL (dissolved in water), Batch #: 270073. The drug was stable until February 1998.
Placebo WAL 801 CL eye drops 0.05%

Animal: Female guinea pigs/Dunkin-Hartley, 19-21 days old, 319-388 g, 5/group

(+) Control: 2,2'-thio-bis(4,6-dichlorophenol), Batch #: 28F0386

Study groups

Group	Treatment	UV irradiation
1	Vehicle (negative) control: placebo for WAL 801 eye drops 0.05%	Yes
2	WAL 801 CL eye drops 0.05%	Yes
3	WAL 801 CL as 5% solution in water	Yes
4	Irritation control: WAL 801 CL as 5% solution in water	No
5	Positive control: 5% 2,2'-thio-bis(4,6-dichlorophenol)	Yes
6	WAL 801 0.05% in water	Yes

The purpose of this study was to evaluate the photosensitizing properties of WAL 801 CL eye drops 0.05% in guinea pigs following dermal administration. The experiment procedure is as follows.

Stage 1 (1st induction, days 1-5): The test substances were applied to the skin on the back region (8 x 6 cm^2) using the patch technique. The patch was placed on the skin for 23 hr, and then the animals were exposed to irradiation using a merry lamp for 10 min. The UV dose was: UVA: 10 J/16.7 mW/cm^2, and UVB: 0.1 J/0.2 mW/cm^2. The animals were treated in this manner once daily for 5 days. Additionally, 4 FCA injections were made to the 4 corners of the application site on days of 1, 3 and 5 of this stage.

Stage 2 (2nd induction, days 16 and 17): Same treatment as in Stage 1 for 2 days.

Stage 3 (challenge, days 31-33): Both flank regions of the animals were depilated. The patch containing the test substance solution was applied to the left flank, and a patch containing the vehicle to the right flank. Positive group used 1% solution of 2,2'-thio-bis(4,6-dichlorophenol) to the left flank and placebo solution to the right flank. The exposure period was 23 hr. UV irradiation was carried out after the exposure as in Stage 1. The treatment was performed once daily for 3 days.

Twenty-four and 48 hr after each treatment stages, and 72-144 hr after the 3rd Stage, the skin reactions were evaluated based on the following point system:

Erythema and eschar formation		Edema formation	
	Value		Value
No erythema	0	No edema	0
Very slight erythema	1	Very slight edema	1
Well-defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

Results:

Under the present test condition, no photosensitizing effects were observed in any WAL 801 CL-treated groups (Groups 2, 3, 4, and 6) and in vehicle control group (Group 1) in guinea pigs. A score of zero was achieved in all drug- and placebo-treated groups. The positive control

group showed a pronounced photosensitizing effect (well-defined to severe erythema, scores 2 to 4). That was seen even during the recovery period (96-122 hr after the 3rd stage).

In conclusion: WAL 801 CL did not possess photosensitizing potential in guinea pigs in this study.

U97-2456: Phototoxicity study of WAL 801 CL eye drops 0.05% by dermal administration to guinea pigs. Vol. 36, Page 187

Key study findings: WAL 801 CL did not possess phototoxic potential in guinea pigs in this study.

Document #: U97-2456
Study Nº: 10276/1/97, A0001013
Conducting laboratory and location: [redacted]

Date of study initiation: April 14, 1997
GLP compliance: Yes
QA report: Yes
Drug: WAL 801 CL eye drops 0.05%, Batch #: 603055. The drug was stable until September 30, 1997.
WAL 801 CL (dissolved in water), Batch #: 270072. The drug was stable until February 1998.
Placebo WAL 801 CL eye drops 0.05%
Animal: Female guinea pigs/Dunkin-Hartley, 28 days old, 328-408 g, 6/group
(+) Control: 8-methoxypsoralen (0.005% in 95% ethanol), Batch #: 104H0042
Route of administration: Dermal

Study groups

Group	N	Treatment		UV irradiation
1	6	Site 1	Placebo for WAL 801 eye drops 0.05%	No
		Site 2	WAL 801 CL eye drops 0.05%	
		Site 3	WAL 801 CL as 5% solution in water	
		Site 4	Positive control: 8-methoxypsoralen	
2	6	Placebo for WAL 801 eye drops 0.05%		Yes
3	6	WAL 801 CL eye drops 0.05%		Yes
4	6	WAL 801 CL as 5% solution in water		Yes
5	6	Positive control: 8-methoxypsoralen		Yes

The purpose of this study was to evaluate the phototoxic properties of WAL 801 CL in guinea pigs following dermal administration. The back region of all animals was prepared for drug administration. For Group 1 animals, the shaven area gave 4 application sites (1.5 x 1.5 cm^2 each) for different treatments. The animals of Groups 2-5 were treated with a single test or control solution. The test substances (25 $\mu l/cm^2$) were applied to the skin (1.5 x 1.5 cm^2) with a micropipette and the sites remained uncovered. Thirty min after dosing, the animals were exposed to a non-erythemogenic dose of UV-irradiation using a merry lamp for 10 min. The UV dose was: UVA: 10 J/16.7 mW/cm^2, and UVB: 0.1 J/0.2 mW/cm^2.

Four, 24, and 48 hr after the irradiation or sham irradiation, the skin reactions were evaluated based on the following point system:

Erythema and eschar formation	Edema formation

	Value		Value
No erythema	0	No edema	0
Very slight erythema	1	Very slight edema	1
Well-defined erythema	2	Slight edema	2
Moderate to severe erythema	3	Moderate edema	3
Severe erythema to slight eschar formation	4	Severe edema	4

Results:

Under the present test condition, no phototoxic effects were observed in any WAL 801 CL-treated groups and in vehicle control group at 4, 24, and 48 hr after dosing in guinea pigs. Animals from Group 1 (treated with WAL 801, placebo, and positive control substance without exposure to UV irradiation) did not show any skin reactions. A score of zero was achieved in all drug- and placebo-treated groups. The positive control group showed a pronounced phototoxic effect (well-defined to severe erythema, scores 2 to 3). In conclusion: WAL 801 CL did not possess phototoxic properties in guinea pigs in this study.

Summary and conclusion:

Four skin sensitization studies were performed with epinastine eye drops. Positive results were noted in only one maximization tests. However, several deficiencies were noted in experimental design, and the study was considered as invalid. Based on the negative obtained from the other maximization tests and the Buehler test, epinastine HCl ophthalmic solution did not have sensitizing potential.

A photosensitizing test and a phototoxicity study with 0.05% epinastine ophthalmic solution in guinea pigs did not reveal any phototoxic properties.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Epinastine is an H_1-receptor antagonist. In pharmacological studies, epinastine showed strong antihistaminic and antiserotonin activities, but the drug had no histamine H_2 antagonistic action and no anticholinergic effects. Epinastine also showed an α-adrenolytic effect.

Epinastine was rapidly absorbed following ocular administration in rabbits and monkeys with very low systemic exposure. High concentrations of radioactivity were measured in the surface tissues (conjunctiva, cornea and sclera) and in pigmented tissues (iris and ciliary body). In *in vitro* studies, epinastine reversibly bound to bovine ocular melanin. In studies conducted in rats and monkeys, the bioavailability of the drug after oral administration was low. Epinastine was distributed throughout peripheral body tissues, but did not cross the blood brain barrier. WAL 801 Cl and its metabolites passed the placental barrier in rat study. The radioactivity was also observed in the milk of lactational rats. The *in vitro* serum protein binding rate was about 60% in rats and 40% in human. Conversion of epinastine to metabolites was similar across animal species tested. Epinastine and metabolites were excreted in urine and feces across animal species. Biliary excretion and entero-hepatic circulation were observed.

In acute systemic toxicity studies in rats, mice and dogs, single dose of epinastine HCl produced several clinical signs (salivation, sedation, emesis, ataxia, and dyspnea). The studies did not reveal any sex specific toxicity or indicate specific target organ of toxicity.

The major findings in repeated dose toxicity studies in rats and monkeys included mortality, decreased body weight gain and decreased food consumption, clinical signs including salivation, emesis, and diarrhea in monkeys, and increased salivary gland weight in rats. The increase in the salivatory gland weight in rats was possibly due to a compensation of the pharmacologically demonstrated α-adrenolytic effect of WAL 801 CL. The NOAELs were 8 mg/kg/day and 10 mg/kg/day in 1-year monkey study and 1-year rat study, respectively.

In both single dose and repeated dose toxicity studies, no specific target organ of toxicity was established. There was a great safety margin between the toxic doses and proposed human daily ocular dose, suggesting that toxicity observed in the systemic toxicity studies would not present a safety concern in clinical human application at the proposed daily ophthalmic dose (0.07 mg/day). The following table shows safety margins between the proposed human ophthalmic dose and the 1-year rat and monkey toxicity study data.

Key findings, systemic exposure and comparative dose of epinastine HCl in animal studies vs. human dose

Species/ treatment duration	Key findings	Dose (mg/kg/day)	Animal/ human ratio	Dose (mg/m^2/day)	Animal/ human ratio	Cmax (ng/ml)	Animal/ human ratio
Rat/1 year	No effect	10 (NOAEL)	7000	60	1160	2.36	56
	↓body weight gain, ↑salivary gland weight	100	70000	600	11600	104	2500
Monkey/1 year	No effect	8 (NOAEL)	5170	96	1850	114.14	2700
	↑salivation, emesis and diarrhea, ↓body weight gain and food consumption	60	42857	720	13900	1790	43000
Human		1.4 μg/kg/day*		0.0518		0.042	

* Human (50 kg) dose was based on 35 μl of 0.05% epinastine HCl instilled in both eyes twice daily.

Acute toxicity studies with impurities and degradation products of the drug specified in this submission showed that these impurities and degradation products did not alter the toxicological profile of epinastine HCl.

Seventeen genotoxicity studies were submitted in the original NDA submission and two more in a supplement. Epinastine HCl was negative in *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamster ovary cells. Epinastine was also negative in a cell transformation assay using Syrian hamster embryo cells, a point mutation assay in V79/HGPRT mammalian cells, and an *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes. Epinastine was negative in Ames tests with *S. typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537, and with *E. coli* strain WP2uvrA. Epinastine in old batches was weakly positive (2-3 folds of vehicle control) in *S. typhimurium* strain TA1538 in two studies conducted in 1980s. TA1538 is not used anymore. It is identical to TA98 except that it lacks the plasmid which gives TA98 error prone repair. Usually a tripling of background was considered as TA1538 positive. In light of negative results in subsequent studies with new batches, the number of revertants of tester strain TA1538 was considered as negative. Positive results were seen in two *in vitro* chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively. In two Ames tests and two *in vitro* chromosomal aberration assays using human lymphocytes conducted

in 2001 to 2003, newly synthesized batches of epinastine did not induce a genotoxic response. The sponsor indicated that "the reason for the negative results in recent batches is presumed to be a consequence of using standardized genotoxicity assay methodology (especially the cytogenetic assay) and use of purer solvents and reagents during the manufacturing process." The reviewer has asked the sponsor to clarify what are the differences between the old and new batches, and what are the differences in the assay methodology.

Carcinogenicity studies were conducted in mice and rats because epinastine HCl The dose selection was not concurred by the agency. The high dose of 40 mg/kg/day, which was not considered as adequate by the reviewer, was selected by the sponsor because it was 200 fold the anticipated human oral dose, which was one of the acceptable criteria for dose selection according to European guidelines when studies were conducted (1986-1988). Epinastine was not carcinogenic at doses up to 40 mg/kg.

Epinastine HCl was not considered as teratogenic in rabbits and rats. However, at 75 mg/kg, total resorption was noted in 3 rabbits and abortion in one rabbit. A decrease in fertility index was seen in HD females (120 mg/kg) in the combined fertility/embryo-fetal development/prenatal and postnatal development study in rats. In the same study, a decrease in pup body weight gain during lactation was observed following an oral dose (120 mg/kg) to female rats from pre-mating to the end of lactation. No drug-related abnormal findings were noted regarding F_0 reproductive parameters, F_1 behavioral parameters, and F_1 fertility parameters in prenatal and postnatal toxicity study.

Several ocular toxicity studies with duration ranging from 1 month to 6 months were conducted in Himalayan rabbits, New Zealand white (NZW) rabbits, and cynomolgus monkeys. Positive responses were only observed in 1-month and 3-month studies in NZW rabbits. In these studies, weak irritant responses evidenced by transient hyperemia and conjunctival discharge were observed after the last daily instillation at concentrations ≥ 0.3% and 0.5% in the 3-month and 1-month studies, respectively. These signs disappeared by the next morning. Histopathological examination showed reduced number and size of epithelial goblet cells and epithelial hyperplasia of the palpebral conjunctiva in drug-treated rabbits. The severity of these changes increased with increasing concentration. A slight decrease in the number and size of epithelial goblet cells was also seen in vehicle control animals in the 3-month study. All conjunctival changes were reversible following a 4-week recovery period.

In two 6-month ocular toxicity studies conducted in NZW rabbits and cynomolgus monkeys, animals were treated at concentrations of 0.05%, 0.1% or 0.5% epinastine, one drop in the left eye (tid). The drug was well tolerated. No toxicologically significant abnormalities were noted. At the highest concentration, 0.5% epinastine, daily AUC exposure in the rabbit and monkey was 8.7-fold human exposure (one drop of 0.05% epinastine in both eyes, bid).

Systemic exposure to epinastine HCl in rabbits and monkeys after 6-month ocular treatment

	Treatment	Dosing frequency	Cmax (ng/ml)	Animal/human	AUC (ng-hr/ml)	Animal/human
Human	0.05%	bid	0.042		0.7	
Rabbit	0.5%	tid	3.25	77	6.1	8.7
Monkey	0.5%	tid	1.51	36	6.1	8.7

The sponsor indicated that positive ocular observations in the 1- and 3-month studies might be artifactual. "The most likely explanation was that rabbit eyes were irritated during the ocular treatment itself, e.g., by the method used to open the conjunctival sac, or perhaps the irritation was caused by a substance in the investigators' gloves. An anomaly based on animal handling would account for the conjunctival hyperemia and discharge, and subsequent histopathological findings, observed in control and drug-treated rabbits." Considering that the weak irritating results from the 1- and 3-month studies were transient, reversible, and not seen in other studies, the reviewer believes that positive observations do not present great safety concerns for the clinical application of the drug product. In conclusion, epinastine HCl eye drops were weakly irritating to rabbit eyes in two studies. In the other ocular toxicity studies in rabbits and monkeys, the drug was well tolerated. Based on nonclinical data, epinastine HCl ophthalmic solution presented no safety concerns regarding its clinical application.

General Toxicology Issues:

Based on nonclinical study results, there are no nonclinical safety concerns relevant to clinical use. No toxicologically significant issues were indicated.

Recommendations:

This application is approvable from a nonclinical perspective with several modifications of labeling as revised in the Carcinogenesis, Mutagenesis, Impairment of Fertility section and Pregnancy section.

Labeling with basis for findings:

Original version:

Carcinogenesis, Mutagenesis, Impairment of Fertility:
In 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses [redacted] negative for mutagenicity in the Ames/*Salmonella* assay and *in vitro* chromosome aberration assay using human lymphocytes. Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine was also negative in the cell transformation assay using Syrian hamster embryo cells, V79/HGPRT mammalian cell point mutation assay, and *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes.
Epinastine had no effect on fertility of male rats [redacted] decreased fertility in female rats at an oral dose up to [redacted] times the MROHD.

Pregnancy: Teratogenic Effects: Pregnancy Category C

[redacted]

In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was [redacted] times the MROHD. [redacted] and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was [redacted] times the MROHD.

Epinastine [redacted]

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, [redacted] ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [redacted] ophthalmic solution is administered to a nursing woman.

Revised version:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In 18-month or 2-year dietary carcinogenicity studies in mice or rats, respectively, epinastine was not carcinogenic at doses *up to 40 mg/kg [approximately 30,000 times higher than the maximum recommended ocular human dose [redacted], of 0.0014 mg/kg/day on a mg/kg basis, assuming 100% absorption in humans and animals].*

Epinastine *in newly synthesized batches* was negative for mutagenicity in the Ames/*Salmonella* assay and *in vitro* chromosome aberration assay using human lymphocytes. *Positive results were seen with early batches of epinastine in two in vitro chromosomal aberration studies conducted in 1980s with human peripheral lymphocytes and with V79 cells, respectively.* Epinastine was negative in the *in vivo* clastogenicity studies, including the mouse micronucleus assay and chromosome aberration assay in Chinese hamsters. Epinastine was also negative in the cell transformation assay using Syrian hamster embryo cells, V79/HGPRT mammalian cell point mutation assay, and *in vivo/in vitro* unscheduled DNA synthesis assay using rat primary hepatocytes.

Epinastine had no effect on fertility of male rats. *Decreased fertility in female rats was observed at an oral dose up to approximately 90,000 times the MROHD.*

Pregnancy: Teratogenic Effects: Pregnancy Category C

In an embryofetal developmental study in pregnant rats, maternal toxicity with no embryofetal effects was observed at an oral dose that was *approximately 150*,000 times the MROHD. *Total resorptions* and abortion were observed in an embryofetal study in pregnant rabbits at an oral dose that was *approximately 55*,000 times the MROHD. *In both studies, no drug-induced teratogenic effects were noted.*

Epinastine reduced pup body weights and body weight [redacted]

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response [redacted] ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: A study in lactating rats revealed excretion of epinastine in the breast milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [redacted] ophthalmic solution is administered to a nursing woman.

X. APPENDIX/ATTACHMENTS:

Addendum to review: No

Other relevant materials (Studies not reviewed, appended consults, etc.): No

Any compliance issues: No

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/s/

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