CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-989

PHARMACOLOGY REVIEW(S)

NDA 20-989

MAY 24 1999

Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

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Draft Completed: 5/24/99

Original Summary
Submission Date: 8/26/98
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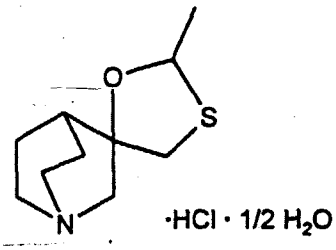
Sponsor: Snow Brand Pharmaceuticals, Inc.

Drug: Cevimeline HCl; cis-2-methylspiro-(1,3-oxathiolane-5,3")-quinuclidine hydrochloride hemihydrate; SNI-2011; AF102B; SND-5008; FKS-508

Structure:



Formulation: Oral Capsules, ——— 30mg:

Ingredient	———	**30mg Capsules (mg per Dosage Unit)**	**Function**
Cevimeline HCl	———	———	Active Ingredient
Lactose Monohydrate, NF	———	———	———
——— Hydroxypropyl Cellulose, NF	———	———	———
Magnesium Stearate, NF	———	———	———

Proposed Indication: Xerostomia ——— in patients with Sjogren's syndrome.

Related Drugs/INDs/NDAs: IND —

Maximum Recommended Dosage of cevimeline HCl: —mg/day (—mg three times daily; —mg/Kg/day in a 60Kg individual).

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1. Pharmacology. Cevimeline is an agonist of muscarinic cholinergic receptors. In Scatchard analyses conducted with rat submandibular salivary gland, cevimeline bound to M_3 receptors (the muscarinic subtype predominant on salivary gland) with an apparent affinity of 1.2μM. Stimulation of M_3 receptors is apparently associated with phosphoinositide metabolism. Cevimeline elicits the actions characteristic of drugs of this class, including salivation, lacrimation, and, at sufficient dosage, diarrhea and tremor. These actions are fully reversible (or preventable) through use of atropine. The drug substance is a racemic modification. (-)-Cevimeline is the active isomer; the (+) stereoisomer has little affinity for muscarinic receptors, does not appreciably antagonize the (-) isomer, and apparently has no biological activity.

2. ADME, Pharmacokinetics. ^{14}C-Cevimeline was rapidly and almost completely absorbed following oral dosing of rats and dogs, with a T_{max} of 30 to 60 minutes. Almost 100% of the activity was excreted in the urine. The elimination half-life was estimated to be one to two hours. Following repeated once-daily dosing of rats, plasma steady-state was reached after the third dose. In single-dose and repeat-dose distribution studies, substantial activity was found in the urinary bladder, preputial gland, cartilage, kidney, intestinal contents, nasal cavity, and trachea. Activity accumulated in the heart, thyroid, cerebellum, skeletal muscle, Harderian gland, and spinal cord, with concentrations in these tissues 3 to 4 times greater following 14 doses than they were after a single dose. However, the material rapidly cleared from these tissues after cessation of dosing.

The metabolism of cevimeline in rats, dogs, and humans is summarized below; in all three species, essentially all clearance is via urine:

Metabolism of Cevimeline. Numbers refer to the Approximate Percentage of an Oral Dose Excreted in the Urine in the Form Indicated.

Species and Gender	Parent Compound (Cevimeline)	Trans-Sulfoxide of Cevimeline	Cis-Sulfoxide of Cevimeline	N-Oxide of Cevimeline	Sulfone of Cevimeline	Glucuronides of Cevimeline and of Trans-sulfoxide Cevimeline
Rat						
Male	8	37	15	17	5	4
Female	14	39	13	16	3	2
Dog						
Male	2	8	6	52	N.D.	15
Female	1	10	7	49	0.1	17
Human						
Male	16	36	9	4	N.D.	22
Female	7	13	3	N.T.	N.D.	N.T.

N.T. = "Not Tested" (the compound was not tested for).
N.D. = "Not Detected"

It is unclear why the human data did not account for a larger fraction of the ingested drug.

3. Toxicology.

3.1 Acute Toxicity.

3.1.1 Acute oral toxicity study of SND-5008 in rats (male), report No. —.86-0014, study report dated 2/20/87, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

Cevimeline HCl was dissolved in water and administered once by intragastric tube to groups of 8 male CrJ:Fisher rats at dosages of 0 (vehicle control group), 100, 110, 120, 132, and 146mg/kg. Surviving animals were maintained for 14 days following treatment. The parameters that were monitored included survival, clinical observations, body weight, food consumption, and gross pathology during necropsy.

Results:

Survival.

Dosage (mg/kg)	Mortality (No. Unsched. Deaths/No. Treated)
0	0/8
100	0/8
110	1/8
120	4/8
132	6/8
146	8/8

Clinical observations. Animals exhibited sedation, convulsions, dyspnea, straub tail, salivation, lacrimation, mydriasis, and diarrhea. Deaths occurred with 30 minutes post-dosing.

Body weight. No remarkable observations.

Food consumption. No remarkable observations.

Necropsy. Animals that died as a result of treatment exhibited blood and fluid in the lungs. No remarkable observations in animals sacrificed on day 14.

Summary/conclusions: The oral LD_{50} in male rats was calculated to be 122mg/kg, with a 95% CI of 116.5-128mg/kg.

3.1.2 Acute oral toxicity study of SND-5008 in rats (female), report No. —86-0009, study report dated 12/20/86, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

Cevimeline HCl was dissolved in water and administered once by intragastric tube to groups of 8 female CrJ:Fisher rats at dosages of 0 (vehicle control group), 104, 118, 136, 156, and 180mg/kg. Surviving animals were maintained for 14 days following treatment. The parameters that were monitored included

survival, clinical observations, body weight, food consumption, and gross pathology during necropsy.

Results:

Survival.

Dosage (mg/kg)	Mortality (No. Unsched. Deaths/No. Treated)
0	0/8
104	3/8
118	6/8
136	8/8
156	8/8
180	8/8

Clinical observations. Animals exhibited sedation, convulsions, dyspnea, straub tail, salivation, lacrimation, mydriasis, and diarrhea. Deaths occurred with 30 minutes post-dosing.

Body weight. No remarkable observations.

Food consumption. No remarkable observations.

Necropsy. Animals that died as a result of treatment exhibited blood and fluid in the lungs. No remarkable observations in animals sacrificed on day 14.

Summary/conclusions: The oral LD_{50} in female rats was calculated to be 108.5mg/kg, with a 95% CI of 100-117mg/kg, although the LD_{50} can only be estimated due to the fact that the dosages studied were too large (too many groups exhibited 100% mortality). However, it is not necessary to determine the LD_{50} to support a NDA.

3.1.3 Acute intravenous toxicity study of SND-5008 in rats (male), report No. 86-0020, study report dated 3/20/87, conducted by [redacted] in compliance with [redacted] Good Laboratory Practice regulations.

Cevimeline HCl was dissolved in 0.9% saline and administered once by IV injection (tail vein) to groups of 8 male CrJ:Fisher rats at dosages of 0 (vehicle control group), 22.5, 33.8, 45, 56.3, and 67.5mg/kg. Surviving animals were maintained for 14 days following treatment. The parameters that were monitored included survival, clinical observations, body weight, food consumption, and gross pathology during necropsy.

Results:

Survival.

Dosage (mg/kg)	Mortality (No. Unsched. Deaths/No. Treated)
0	0/8
22.5	0/8
33.8	0/8
45	3/8
56.3	7/8
67.5	7/8

Clinical observations. Animals exhibited sedation, convulsions, dyspnea, straub tail, salivation, lacrimation, mydriasis, and diarrhea. Deaths occurred with 30 minutes post-dosing.

Body weight. No remarkable observations.

Food consumption. No remarkable observations.

Necropsy. Animals that died as a result of treatment exhibited blood and fluid in the lungs. No remarkable observations in animals sacrificed on day 14.

Summary/conclusions: The IV LD_{50} in male rats was estimated to be 49.7mg/kg, with a 95% CI of 44-55mg/kg.

3.1.4 Acute intravenous toxicity study of SND-5008 in rats (female), report No. —86-0021, study report dated 4/10/87, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

Cevimeline HCl was dissolved in 0.9% saline and administered once by IV injection (tail vein) to groups of 8 female CrJ:Fisher rats at dosages of 0 (vehicle control group), 30.6, 39.4, 48.1, 56.9, and 65.6mg/kg. Surviving animals were maintained for 14 days following treatment. The parameters that were monitored included survival, clinical observations, body weight, food consumption, and gross pathology during necropsy.

Results:

Survival.

Dosage (mg/kg)	Mortality (No. Unsched. Deaths/No. Treated)
0	0/8
30.6	0/8
39.4	1/8
48.1	6/8
56.9	8/8
65.6	8/8

Clinical observations. Animals exhibited sedation, convulsions, dyspnea, straub tail, salivation, lacrimation, mydriasis, and diarrhea. Deaths occurred with 30 minutes post-dosing.

Body weight. No remarkable observations.

Food consumption. No remarkable observations.

Necropsy. Animals that died as a result of treatment exhibited blood and fluid in the lungs. No remarkable observations in animals sacrificed on day 14.

Summary/conclusions: The IV LD_{50} in female rats was estimated to be 44.8mg/kg, with a 95% CI of 42-48mg/kg.

3.2 Multiple Dose Toxicity.

3.2.1 One year oral toxicology study of FKS-508 in rats, report No. —89-2342, study No. —89-2342, start date 9/1/89, study report dated 10/25/91, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

Cevimeline HCl was dissolved in water and administered by gavage once daily to four groups of SPF F344/DuCrj rats at dosages of 0 (vehicle control), 1, 6, and 36mg/kg/day for one year; each "group" contained 20 animals of each gender. In addition, groups of "satellite" animals were similarly treated (5 control animals of each sex and 45 animals of each gender at each treatment level. The satellite animals were sacrificed at interim points during the study for toxicokinetic analysis and for assessment of hematological and blood chemistry changes. The dosages were selected based upon data from a 13-week study, and are compared to the maximum proposed clinical dosage below:

Table 3.2.1-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of 3mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of human dose (based on body weight)	Multiple of human dose (based on body surface area)
I	0	0	0
II	1	0.3	0.05
III	6	2	0.3
IV	36	12	2

The parameters that were monitored included survival, clinical observations, body weight, food consumption, ophthalmology, clinical pathology (blood chemistry, urinalysis, and hematology), gross pathology during necropsy, organ weights, and histopathology of a full range of tissues (including electron microscopy of sections of liver and kidney); histopathology was only performed on control and high-dose animals and gross lesions, as well as the pancreas and salivary glands from all groups. Toxicokinetic data were obtained at 30 minutes and at 6 hours after dosing on the first day of treatment, and during weeks 4, 13, 26, and 52 of treatment.

Results:

Survival. One male and six females at 36mg/kg/day were either found dead or were sacrificed prior to the scheduled termination due to toxicity. No test-substance-related deaths occurred in any other groups.

Clinical observations. 1mg/kg/day was a NOEL. A few animals of each gender exhibited mydriasis at 6mg/kg/day. At 36mg/kg/day,

both males and females exhibited mydriasis, salivation, lacrimation, soft stools, clonic/tonic convulsions, "standing on tiptoe", dyspnea, and perigenital staining.

Body weight. No remarkable observations.

Food consumption. No remarkable observations.

Ophthalmology. No remarkable observations.

Blood chemistry. No remarkable observations.

Hematology. No remarkable observations.

Urinalysis. No remarkable observations.

Organ weights.
Males and females: Increased mean salivary gland weight and increased mean adrenal weight at 36mg/kg/day only, a trend toward increased liver weight in all treatment groups (but none statistically significant), and slightly increased mean pancreatic weight in all treatment groups.

Females only: Slight, but statistically significant, increase in mean kidney weight at 36mg/kg/day.

Gross pathology. Although isolated instances of abnormal observations were reported, it is unclear if they were related to treatment. The incidence of these findings seems to have been slightly higher in the high-dose group (usually only involving one or two animals, however), and included red or black spots in the glandular stomach (2 males and 1 female), a cyst or swelling of the hypothesis (1 male only of both the mid and high-dose groups), unilateral cataract of 1 male and 1 female in the high-dose group), nodular endometrial hypertrophy in the uterine horn of 1 high-dose female, and a thoracic subcutaneous tumor in 1 high-dose male. These are probably irrelevant findings.

Histopathology. Hypertrophy of the acinar cells was observed in the salivary glands and pancreas of both male and female high-dose animals. No other remarkable observations were made.

Toxicokinetic data. The plasma concentration of cevimeline was proportional to dosage over the range studied. The drug substance was apparently rapidly cleared, approaching 0 by 6 hours after dosing. No gender related differences in plasma levels were apparent. The AUC was not calculated.

Summary/conclusions: Six out of 20 females that received 36mg/kg/day cevimeline died or were sacrificed prematurely (as

well as one high-dose male). The cause of the deaths was not identified. However, in view of the fact that both rats and mice tolerated substantially higher dosages in two-year studies with no decrease in survival relative to controls (see section 3.5 of this review), it seems doubtful that the deaths seen in this study were actually due to treatment. Some of the animals experienced convulsions (presumably due to excessive cholinergic stimulation of the CNS as a result of the pharmacologic activity of the drug substance), and it is possible that the deaths were directly or indirectly the result of this stimulation. Other pharmacologic (cholinergic) actions of cevimeline were apparent at 6mg/kg/day and above, including mydriasis, salivation, lacrimation, and soft stools. The mean weight of the pancreas (both absolute and relative to body weight) was slightly increased in all treatment groups, which presumably correlates with the pancreatic acinar cell hypertrophy observed in high-dose animals. The effect was small, and was apparently due to muscarinic stimulation. However, because of the pancreatic effects, a NOAEL was not observed in this study.

Reviewer's Note: *The dose-multiples achieved in this study (see Table 3.2.1-1, above) were less than would be desired in a study of this type. Both the low-dose and the mid-dose were multiples of less than one after normalizing the data on the basis of body surface area, and the high-dose, which may have reduced survival, was only twice the maximum daily clinical dose (after normalizing for surface area). However, several extenuating factors exist which should be borne in mind while interpreting these results: 1) the dose-limiting "toxicities" are manifestations of the pharmacodynamic effects of cevimeline (it's a cholinomemetic); 2) these adverse (cholinergic) effects are well studied and easily monitored in patients; 3) no evidence was obtained of toxicity not related to stimulation of muscarinic receptors; and 4) no decrease in survival was associated with substantially higher dosages in both rats and mice in two-year carcinogenicity bioassays (see section 3.5 of this review). When considered in light of the other available nonclinical and clinical data, I consider this study to be acceptable as a pivotal chronic toxicology study in support of NDA 20-989.*

3.2.2 One year oral toxicology study of FKS-508 in Beagle dogs, report No. ——28914, study No. 28914, study report dated 10/7/91, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

Cevimeline HCl was administered in capsules by mouth once daily to four groups of 5 month old Beagle dogs at dosages of 0 (empty capsules), 0.5, 3, and 18mg/kg/day for one year; each "group" contained 4 animals of each gender. The dosages were

selected based upon data from a 13-week study, and are compared to the maximum proposed clinical dosage below:

Table 3.2.2-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of 3mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of human dose, (based on body weight)	Multiple of human dose (based on body surface area)
I	0	0	0
II	0.5	0.2	0.1
III	3	1	0.5
IV	18	6	3

The parameters that were monitored included survival, clinical observations, body weight, food consumption, ophthalmology, clinical pathology (blood chemistry, urinalysis, and hematology), ECG, liver and renal function tests (clearance of indocyanine and phenolsulfonphthalein, respectively), gross pathology during necropsy, organ weights, and histopathology of a full range of tissues. Toxicokinetic data were obtained at 1, 6, and 24 hours after dosing on the first day of treatment, and during weeks 4, 13, 26, and 52 of treatment.

Results:

Survival. No unscheduled deaths occurred.

Clinical observations. 0.5mg/kg/day was a NOEL. At 3mg/kg/day and above, signs of excessive cholinergic stimulation occurred, including salivation, diarrhea, and lacrimation. Tremor was observed in the high-dose group (18mg/kg/day) only.

Body weight. No remarkable observations.

Food consumption. No remarkable observations.

Water consumption. No remarkable observations.

Ophthalmology. No remarkable observations.

Blood chemistry. No remarkable observations.

Hematology. No remarkable observations.

Urinalysis. No remarkable observations.

Liver function test. No effect of treatment.

Renal function test. No effect of treatment.

ECG. Females at 18mg/kg/day exhibited a slight prolongation of the P-R interval; this was probably a result of cholinergic stimulation of the heart.

Organ weights. No remarkable observations.

Gross pathology. No remarkable observations.

Histopathology. No remarkable observations.

Toxicokinetic data. The plasma concentration of cevimeline was proportional to dosage over the range studied. The drug substance was apparently rapidly cleared, with the value at 6 hours only about one-tenth the value at 1 hour post-dosing. By 24 hours after dosing the levels were approaching 0. No gender related differences in plasma levels were apparent. The AUC was not calculated.

Summary/conclusions: Cevimeline induced toxicity at 18mg/kg/day (high-dose group), as evidenced by the induction of tremors, which were presumably due to excessive cholinergic stimulation of the CNS as a result of the pharmacologic activity of the drug substance. Other pharmacologic (cholinergic) actions of cevimeline were apparent at 3mg/kg/day and above, including salivation, lacrimation, and soft stools. Increased duration of the P-R interval was observed in females at 18mg/kg/day, and this presumably was also a consequence of the cholinomemetic properties of the drug. I consider 3mg/kg/day to have been a NOAEL (possibly 18mg/kg/day as well), and 0.5mg/kg/day to have been a NOEL.

Reviewer's Note: *See note under section 3.2.1, above, for discussion of the small dose multiples.*

3.3 Reproductive Toxicology.

3.3.1 Fertility and general reproductive performance study of SND-5008 in rats (treated males x treated females), report No. 87-0001, study No. 87-0001, in-life 10/87-11/87, study report dated 5/31/88, conducted by [redacted] in compliance with [redacted] Good Laboratory Practice regulations.

Sprague-Dawley rats were utilized in this study. The animals were acclimated for 14 days prior to use. The F0 generation involved 4 groups of 48 rats each (24 male and 24 female); the rats were orally dosed with either 0 (vehicle control), 0.2, 3, or 45mg/kg/day cevimeline HCl. The dosages used in this study are compared to the maximum clinical dosage in Table 3.3.1-1

Table 3.3.1-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of 3mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of human dose (based on body weight)	Multiple of human dose (based on body surface area)
I	0	0	0
II	0.2	0.07	0.01
III	3	1	0.16
IV	45	15	2.4

The drug substance was dissolved in water. Males were dosed for 63 days prior to mating, and treatment continued until sacrifice. Females were dosed for 14 days prior to mating, and treatment continued until day 7 of gestation. At the conclusion of the pre-treatment period, 1 male and 1 female from the same dosage group were cohabitated. Females were presumed pregnant if a vaginal plug was observed or if sperm were observed in a vaginal smear. The parameters that were monitored included body weight and food consumption. The females were sacrificed and necropsied on day 20 of gestation; the ovaries and uterus were examined for numbers of corpora lutea, implantations, resorptions, live and dead fetuses, external anomalies, fetal body weight, etc. Sperm morphology/motility data were not generated.

Results.

Survival. One high-dose male convulsed and died 2 minutes after treatment on day 40. One high-dose females died on the 22nd day of treatment (5th day of pregnancy). No other unscheduled deaths occurred.

Clinical signs. No abnormal signs occurred in animals at 3mg/kg/day or less. At 45mg/kg/day, signs observed in both

genders included convulsions, salivation, mydriasis, lacrimation, diarrhea.

Body weight. Mean body weights of males at 3mg/kg/day and above were reduced. Females at 45mg/kg/day exhibited a slight (but statistically significant) reduction in the mean body weight during the final two weeks of pregnancy.

Reproductive parameters. All control females became pregnant, while one female in each of the low and mid-dose groups and two females in the high-dose group failed to become pregnant. No significant differences were found in the mean numbers of corpora lutea, the percentage of fetuses dead or resorbed, the mean number of live fetuses, or the mean placental weight. The mean number of implantations was significantly reduced in high-dose animals (12.4±2.5 vs. 14.6±1.4 in controls), and the mean fetal body weight was slightly higher in the high-dose group. The percentage of fetuses with skeletal variations increased slightly with increasing dosage (6%, 5%, 10%, and 14% of fetuses in the control, low, mid, and high-dose groups, respectively). Three fetuses in the high-dose group exhibited abnormalities of the viscera (one occurrance each of "dilation of the lateral ventricle", "unilateral anophthalmia", and "thymic remnant in the neck"), accounting for 4% of the fetuses examined, as opposed to none in the control group.

Conclusion: Cevimeline apparently did not adversely effect reproductive performance or fertility of male animals. Females in the high-dose group exhibited a statistically significant reduction in the mean number of implantations. A small (and apparently non-significant) increase in the incidence of minor fetal anomalies was induced, which may have been secondary to "non-specific" stress of the dams (as a result of excessive cholinergic stimulation), rather than a specific teratogenic effect of the test material. The fetal effects will not be analyzed by litter or mentioned in the label because the change in incidence was slight and apparently did not differ significantly from the control values. See sections 3.3.2 and 3.3.3 of this review for further data concerning teratology of cevimeline (when administered during the period of organogenesis).

3.3.2 Teratology study of SND-5008 in rats, report No. —86-0003, study No. —86-0003, in-life circa 3/87, study report dated 5/31/88, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

This study was conducted to assess the developmental effects, if any, of cevimeline HCl when administered to pregnant rats during the period of organogenesis.

Sprague-Dawley rats were utilized in this study. The F0 females (10 weeks old) were caged overnight 1:1 with males (15 weeks old). The day on which a positive vaginal smear was obtained was designated as day 0. The females were assigned to groups of 39 (control and low-dose) or 38 mid and high-dose) presumed-to-be-pregnant rats each and were dosed with either 0 (vehicle (water) control), 5, 30, or 60mg/kg/day cevimeline HCl, administered by gavage on days 7 through 17 of gestation. The dosages used in this study are compared to the maximum clinical dosage in Table 3.3.2-1.

Table 3.3.2-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of 3mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of human dose (based on body weight)	Multiple of human dose (based on body surface area)
I	0	0	0
II	5	1.7	0.27
III	30	10	1.6
IV	60	20	3.2

The test solutions were demonstrated to be stable under the conditions of use. Approximately 25 females from each group were sacrificed and cesarean sectioned on day 20, while the remainder were permitted to deliver and rear the F1 animals, and were killed on day 22 following delivery. The standard parameters were monitored, including clinical signs, body weight, food consumption, gross pathology during necropsy, numbers of resorptions, corpora lutea, external, visceral, and skeletal malformations and variations, etc.

F1 animals that were allowed to be delivered (pups) were initially assessed for viability, body weight, behavior, and development. Selected F1 animals were tested in a battery of standardized tests for defects in memory, cognition, coordination, etc. F1 animals autopsied at 10 weeks of age were examined microscopically for the presence of spermatozoa in testis sections and for the formation of follicles and corpora lutea in ovaries of females. One F1 animal of each gender from each litter was paired with an animal of opposite gender at 10 weeks of age and allowed to mate. Again, the standard reproductive parameters were monitored, and the pregnant F1 animals were sacrificed and cesarean sectioned on day 20.

Results.

A. F0 generation:

Clinical signs and survival: No test-material related effects in the control group or the low-dose group. At 30mg/kg/day, salivation, mydriasis, lacrimation, prone positioning, and

diarrhea were observed. At 60mg/kg/day, in addition to the signs seen at 30mg/kg/day, tremor and convulsions occurred immediately following dosing in 5 animals, and two animals died following repeated convulsions.

Body weight: No remarkable observations.

Food consumption: No remarkable observations.

Observations made following cesarean section: Treated animals tended to exhibit a slightly higher incidence of dead or resorbed fetuses, although statistical significance was only observed in the low-dose group. The mean body weight of both male and female fetuses was slightly but statistically significantly reduced in all three treatment groups on the day of birth, but this effect was very small and was reversed within 24 hours, and is therefore considered to have been inconsequential.

B. F1 generation:
Fetal morphological observations: No remarkable findings were made in regard to external, visceral, or skeletal malformations or variations.

Mean pup weight: As mentioned above, the mean body weight of both male and female fetuses was slightly but statistically significantly reduced in all three treatment groups, but this "effect" was reversed within 24 hours. No treatment-related differences in mean pup weight were apparent throughout the remainder of the observation period (77 days).

Pup viability: No significant differences.

Clinical signs: No remarkable effects.

Developmental landmarks and functional testing: No remarkable findings.

Behavior, learning and memory ability: No remarkable findings.

Growth and development: No remarkable findings.

Gestation, parturition, and lactation: Although the differences were not statistically significant, F1 animals associated with the "high-dose" group seemed to require more attempts to successfully copulate or become pregnant, exhibited lower mean body weight during the latter five days of pregnancy, and exhibited smaller mean numbers of implantations, and a larger percentage of dead or resorbed fetuses.

Necropsy: No remarkable observations were made during necropsy.

C. F2 generation:
Pup viability and clinical signs: Litter size and pup viability were similar in all groups.

Body weight: No remarkable findings.

Necropsy: No remarkable macroscopic observations were made during necropsy.

Conclusion: Administration of cevimeline to pregnant rats (days 7 through 17) induced salivation, mydriasis, lacrimation, prone positioning, and diarrhea in F0 animals at 30mg/kg/day, and (in addition to those signs) induced tremor and convulsions in F0 animals at 60mg/kg/day. No effect of treatment was apparent on the F1 or F2 animals. Under the conditions of this study, cevimeline did not appear to exert developmental effects upon rats, with the exception of statistically significantly reduced mean birth weight of the F1 pups at all dosages studied. This effect was reversible. It is concluded that this study suggests that cevimeline would not be a teratogen in humans when administered during the period of organogenesis.

3.3.3 Teratology study of SND-5008 in rabbits, report No. ——— 319-262B, study No. ——— -319-262B, in-life circa 3/87, study report dated 11/30/87, conducted by ——————————— ——————— in compliance with ——— Good Laboratory Practice regulations.

This study was conducted to assess the developmental effects, if any, of cevimeline when administered to pregnant rabbits during the period of organogenesis.

New Zealand albino rabbits were utilized in this study; the animals were approximately 27 weeks of age at the time of breeding. The animals were paired, allowed to copulate, and the presence of spermatozoa in a vaginal smear taken as evidence of successful mating. The presumed-to-be-pregnant females were randomly assigned to one of four groups, each group containing 12 to 15 animals, and were dosed by gavage with either 0 (vehicle (water) control), 0.2, 3, or 45mg/Kg/day cevimeline. The dosages used in this study are compared to the maximum clinical dosage in Table 3.3.3-1.

Table 3.3.3-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of 3mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of human dose (based on body weight)	Multiple of human dose (based on body surface area)
I	0	0	0
II	0.2	0.07	0.02
III	3	1	0.3
IV	45	15	5

The cevimeline was administered on days 6 through 18 of gestation. All surviving rabbits were euthanized on gestation day 29 and subjected to necropsy (including cesarean section).

Results.

Survival and pregnancy status: No treatment-related deaths or abortions occurred. Apparently all F0 females were actually pregnant.

Clinical signs: No treatment-related clinical signs were reported in animals at 0.2 or 3mg/kg/day. At 45mg/kg/day, observed signs included salivation and tachypnea.

Body weight: No remarkable observations.

Food consumption: The data suggest a trend toward decreased food consumption in animals at 45mg/kg/day, but the difference was not statistically significant.

Necropsy: No treatment-induced lesions were observed in any F0 rabbits during necropsy.

Observations made following cesarean section: No remarkable findings in any of the standard parameters (resorptions, percentage of fetuses viable, fetal body weight, or external, skeletal, or visceral malformations or variations).

Conclusion: Oral administration of cevimeline to pregnant rabbits (days 6 through 18) produced no apparent toxicity in either F0 or F1 animals. The maximum dosage used (45mg/kg/day) was a NOAEL in regard to maternal and fetal toxicity (with the exception of cholinergic stimulation), and is an acceptably large multiple of the maximum proposed human dose (about 5 times the human dose following normalization for body surface area). It is concluded that this study suggests that cevimeline would not be a teratogen in humans when administered during the period of organogenesis.

3.3.4. A Reproduction Toxicity Study of FKS-508 in Rats by Oral Administration During Perinatal and Lactation Periods, study No. 90-0001, in-life 5/90-9/90, report dated 2/28/91, conducted by [redacted] in compliance with Good Laboratory Practice regulations.

This study was conducted to evaluate the potential of cevimeline HCl to influence F0, F1, or F2 animals when administered to F0 dams from late pregnancy through the period of lactation. Pregnant Sprague Dawley SPF rats received by gavage cevimeline dissolved in water at dosages of 0 (vehicle control), 3, 12, or 45mg/Kg/day beginning on day 17 of gestation and continuing until day 20 postpartum (approximately from closure of the hard palate until the time of weaning). The dosages used in this study are compared to the maximum clinical dosage in Table 3.3.4-1.

Table 3.3.4-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of 3mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of human dose (based on body weight)	Multiple of human dose (based on body surface area)
I	0	0	0
II	3	1	0.16
III	12	4	0.65
IV	45	15	2.4

The dosage selection was based on observations made in teratology and fertility studies in rats. Each of the four treatment groups contained 24 F0 animals. Litters were randomly culled to 8 pups on day 4 postpartum. Dams were sacrificed on day 21 postpartum and subjected to necropsy. F1 animals were observed for growth and development, including body weight gain, morphological parameters (ear separation, incisor eruption, opening of the eyes and vagina, testicular descent), a standard battery of functional (reflex) tests, and behavior and learning tests (open field test, Rotarod test, a conditional avoidance test, a water maze test). One male and one female F1 animal from each F0 dam were assessed for reproductive function; pregnant F1 animals were sacrificed on day 20 of gestation and the standard cesarean section data were obtained.

Results.

A. F0 dams.

Mortality/clinical signs. Two F0 animals at 45mg/kg/day died; one on day 0 postpartum (the fourth day of treatment) and one on day 5 postpartum; these animals exhibited salivation, mydriasis, and tonic convulsions. Animals at 45mg/kg/day exhibited occasional episodes of mydriasis, salivation, lacrimation, "prone

position", soft stools, and convulsions. At 12mg/kg/day, slight mydriasis and salivation were sporadically observed. No remarkable clinical signs were observed at 3mg/kg/day.

Body weight and food consumption. Animals that received cevimeline exhibited statistically significant reductions in mean body weight and food consumption beginning the last few days of pregnancy and continuing throughout the period of lactation.

Delivery and nursing. The duration of gestation was slightly (but statistically significantly) prolonged in animals at 45mg/kg/day. No differences in the rate of stillbirths or the mean litter size were observed at any dose.

F0 organ weight data. Statistically significant differences were observed in some mean organ weight values obtained from animals at 45mg/kg/day, including increased absolute and relative (to body weight) values of the adrenals, decreased absolute and relative values of the thymus, decreased absolute heart weight, and increased relative weight of the lungs, brain, and liver.

B. F1 data.

Survival. An apparent increase in the mortality rate of F1 animals was observed in the 45mg/kg/day group during the first 4 days postpartum (1, 4, 1, and 9 deaths at 0, 3, 12, and 45mg/kg/day, respectively), although the difference was not statistically significant. No increase in the mortality rate was apparent between days 4 and 20 postpartum.

Weight gain of F1 animals. F1 animals in the high-dose (45mg/kg/day) group exhibited mean body weights that were statistically significantly lower than control F1 animals from day 0 through day 42 postpartum, but did not differ from control values on days 49 through 77 (date of terminal sacrifice).

Gross malformations. No remarkable observations.

Development. No remarkable differences were observed between groups in regard to morphodifferentiation, including pinnae separation, appearance of abdominal hair, eruption of incisors, opening of the eyelids, descent of the testes, or opening of the vagina.

Performance in open field tests. No remarkable observations were made in regard to reflexes or performance in the Rotarod test, a water maze, or a conditional avoidance test.

Mating rate, fertilization rate, and conception rate of F1 animals. No remarkable observations.

Body weights of F1 dams during gestation. No remarkable observations.

Cesarean section findings in F1 dams. No remarkable observations.

C. F2 data.

External observations of F2 animals. No remarkable observations.

Body weights of F2 animals. No remarkable observations.

Summary/Discussion: Under the conditions of this study, cevimeline appeared to cause no substantial adverse effects on reproduction or developmental parameters of F0, F1, or F2 animals at dosages of 45mg/kg/day (the highest dosage explored) or less when administered PO to the F0 animals only on the last 3 days of gestation and the first 20 days postpartum, with the possible exception of a slight increase in the duration of the gestation period of F0 dams. A reduction in the mean body weight and food consumption were observed in F0 animals at all levels of exposure to cevimeline that were used in this study. Administration of 45mg/kg/day resulted in an increased rate of mortality and adverse clinical signs in F0 dams, a reduced rate of body weight gain in F1 animals (as well as in F0 animals), and statistically significant differences in certain mean organ weights in F0 animals.

3.4 Genetic Toxicology.

3.4.1 Reverse mutation studies of SND-5008 in bacterial auxotrophic mutants, Salmonella typhimurium and Escherichia coli, study No. —'87-0004, in-life 9/87, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and E. coli strain WP-2 (uvrA⁻) were plated with cevimeline HCl; the amount of test material per plate ranged from ——— Assays were conducted with and without metabolic activation (S9). Appropriate positive control compounds were used.

Results. No significant increase in the reverse mutation rate was observed at any concentration of test material, in either the presence or absence of S9. Appropriate responses were induced by the positive control substances.

Conclusions. This study provided no evidence that the test material was mutagenic.

3.4.2. Chromosomal aberration studies on SND-5008 using mammalian cells cultured, *in vitro*, study No. — 87-0006, in-life 12/87, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

Cevimeline HCl was assayed for the ability to induce chromosomal aberrations in cultured fibroblasts derived from lung tissue of a newborn Chinese hamster (CHL cells), both in the presence and in the absence of metabolic activation (S9). The cells were exposed to cevimeline in concentrations ranging up to 2.5mM in assays conducted without S9 and up to 10mM with S9 according to standard procedures (maximum concentrations selected on the basis of growth inhibition in preliminary assays). Appropriate controls were used. All cultures were treated with colchicine prior to harvest. Prepared slides were examined for chromosomal aberrations.

Results. Exposure to cevimeline did not increase the frequency of occurrence of chromosomal aberrations, either with or without metabolic activation. The positive control compounds did significantly increase the incidence of chromosomal aberrations.

Conclusions. These data suggest that cevimeline is not clastogenic.

3.4.3 Mutation study of AF102B at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells using the ——— technique, study No. — 97-0005, in-life 3/98, conducted by ——— in compliance with ——— Good Laboratory Practice regulations.

This test system is based on detection and quantitation of forward mutation of mouse lymphoma L5178Y cells to a genotype that is deficient for thymidine kinase. L5178Y cells are heterozygous at the thymidine kinase locus (TK +/-). The cells

were cultured in the presence of cevimeline in concentrations ranging from 0 to 5mg/ml. Following exposure to the test substance for 3 hours, the cells were washed and then cultured for 48 hours without cevimeline. Cells were then cultured in the presence of 5-trifluorothymidine (TFT). TFT is lethal to cells that express thymidine kinase, and therefore selects for new TK -/- mutants. The number of colonies that grow on the selective medium is (theoretically) proportional to the potential of the test substance to cause genetic toxicity. Two independent assays were conducted with and without metabolic activation (S-9). Appropriate controls were used.

Results. The mean mutation frequency of cells exposed to the test substance did not differ significantly from the negative controls. Significant differences were obtained with the positive controls.

Conclusions. These data suggest that the test substance is not mutagenic.

3.4.4 Micronucleus test of FKS-508, study No. — 88-0004, in-life 1/89, conducted by ———— , in compliance with ———— Good Laboratory Practice regulations.

Cevimeline was assessed for effect on the incidence of micronucleated polychromatic erythrocytes in male ICR mice. The animals each received a single oral dose of either 17.5, 35, or 70mg/kg cevimeline, water (negative control), or 2mg/kg mytomycin C (positive control). Bone marrow smears were obtained from negative control and cevimeline-treated mice at 24, 48, and 72 hrs. post-dosing; positive controls were sacrificed at 24 hrs. only. Six animals were sacrificed at each treatment-level/time point. The smears were processed and examined for the number of micronucleated cells per 1000 polychromatic cells examined; the ratios of polychromatic to normochromatic erythrocytes were recorded.

Results. No statistically significant differences were observed between the test substance and the negative control. A significant increase in the occurrence of micronucleated cells relative to the number of polychromatic erythrocytes was observed in smears from positive control animals.

Conclusions. These data suggest that the test substance is not clastogenic.

3.5 Carcinogenicity.

3.5.1. AF102B oncogenicity study by dietary administration to CD-1 mice for 104 weeks, study No. [redacted]'007/982285, in-life 8/95-8/97, study report dated 7/7/98, conducted by [redacted] in compliance with [redacted] Good Laboratory Practice regulations.

This study involved 4 groups (dosage levels) of CD-1 mice [redacted], each group initially containing 52 males and 52 females. The animals consumed feed that contained cevimeline HCl, resulting in approximate dosages of 0 (controls), 75, 150, or 300mg/Kg/day, 7 days per week until termination, with the exception that males receiving 300mg/Kg/day were switched to plain diet (no cevimeline) after 85 weeks of treatment because survival in that group had reached 25 animals. The remaining high-dose males were not sacrificed until week 100, when survival reached 20 animals. Surviving males in the other three main-study groups were sacrificed after 102 weeks of treatment. All surviving main-study females were sacrificed after 104 weeks of treatment. These dosages were recommended by the exec. CAC following review of dose-ranging data (exec. CAC report dated 6/13/95). The exec. CAC also approved the termination of treatment of the high-dose males when survival reached 25 animals and sacrifice of these animals when survival reached 20 animals (exec. CAC report dated 5/13/97). An additional 30 animals of each gender were maintained on feed at each of the three treatment groups (75, 150, or 300mg/Kg/day) for the purpose of toxicokinetic analysis; blood samples were obtained from 6 of these animals of each gender at 4 to 6 hour intervals (5 time points during a selected day) following 13, 26, and 52 weeks of exposure. The dietary concentrations of cevimeline HCl were adjusted on the basis of body weight and food consumption data to provide the estimated dosage; fresh food was prepared weekly for the first 14 weeks and every 2 weeks thereafter. Appropriate analyses of the feed were performed to ensure that the concentration and stability of cevimeline in the feed were suitable. In Table 3.5.1-1, the dosages of cevimeline used in this study are compared to the maximum dosage of cevimeline recommended (for a 60Kg individual) in the draft label of the product (-mg/Kg/day).

Table 3.5.1-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of -mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of Human Dose (Based on Body Weight)	Multiple of Human Dose (Based on Body Surface Area)	Multiple of Human Dose, Male Mice (Based on $AUC_{0-\infty}$)*	Multiple of Human Dose, Female Mice (Based on $AUC_{0-\infty}$)*
I	0	0	0	0	0
II	75	25	2	2	1
III	150	50	4	4	2
IV	300	100	8	9	6

*$AUC_{0-\infty}$ for a patient at the maximum proposed dosage is approximately 2000ng•hr/mL. Values are based on the AUC data presented in Table 3.5.1-3, below.

The parameters that were monitored included survival, clinical observations, body weight, food consumption, blood chemistry, hematology (including leukocyte differential), gross pathology, and organ weights. Histopathology was performed on the following tissues:

Adrenals (cortex and medulla)
Aorta
Brain
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes and optic nerve
Femoral bone and marrow
Gall bladder
Heart
Ileum
Jejunum
Kidneys
Liver
Lungs with bronchi
Lymph nodes (mandibular and mesenteric)
Mammary gland
Ovaries
Pancreas
Pituitary
Prostate
Rectum
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle

Skin
Smooth muscle
Spinal cord
Spleen
Sternum
Stomach
Testes
Thymus
Thyroid (with parathyroids)
Tongue
Trachea
Urinary bladder
Uterus with cervix
Vagina

And any gross lesions. Histopathology was performed on these tissues from all animals in groups I and IV (control and high-dose), all male animals in group III, and from animals found dead or sacrificed prematurely. In addition, the adrenals, pancreas, submandibular salivary gland, gross lesions, and "target organs" (organs in which lesions were observed in high-dose animals (lungs)) were histologically examined from group II and III animals.

Results.

Actual mean exposure levels. Based on body weight and food consumption data, the mean intakes of cevimeline HCl for the four groups were estimated; these data are presented in Table 3.5.1-2.

Table 3.5.1-2. Mean Dosages Actually Achieved (mg/Kg/day)

Group	Theoretical Dosage		Actual Mean Dosage	
	Males	Females	Males	Females
I	0	0	0	0
II	75	75	75.4	75.4
III	150	150	151.6	151.6
IV	300	300	300.1	300.7

Toxicokinetic data. AUC values calculated from samples obtained during week 52 are indicated in Table 3.5.1-3; similar values were obtained during weeks 13 and 26. Exposure increased roughly in proportion to dosage, with males experiencing a greater level of exposure at a given dosage.

Table 3.5.1-3. AUC Values from Week 52

Group	AUC (ng•h/mL)	
	Males	Females
I	NA	NA
II	3527	2128
III	7957	4664
IV	18802	12624

Survival. The survival data are presented in Table 3.5.1-4.

Table 3.5.1-4. Survival Rates of Mice at Terminal Sacrifice

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Number of Males that Survived to the Scheduled Sacrifice*	Number of Females that Survived to the Scheduled Sacrifice
I	0	23	29
II	75	20	21
III	150	22	28
IV	300	20	30

*Note: As described above, the "scheduled" sacrifice point for the males was redefined on the basis of survival, and was less than 104 weeks.

Clinical observations. The only observation that was considered to be related to treatment was yellow staining (poor grooming), observed in males at 150mg/Kg/day and both genders at 300mg/Kg/day.

Body weight. Mean body weight and mean body weight gain were reduced in a dose-dependent manner in both males and females; statistically significant differences in weight gain were observed in both genders at 150mg/Kg/day and above.

Food consumption. Mean food consumption tended to be slightly reduced in both males and females at 150mg/Kg/day and above.

Clinical pathology. A few anomalous clinical pathological values were obtained, but the meaning of these findings in two-year old mice is unclear.

Organ weights. Following normalization of the organ weight data to account for differences in body weight, apparent trends included increased mean heart, kidney, lung, and adrenal weights in both genders, and increased liver weight in females. Some of the differences achieved statistical significance, but the magnitudes of most of the differences were small, and it is unclear if the differences were biologically meaningful.

Gross pathology. A statistically significant increase in the incidence of masses in the lungs was reported in females; the lung-mass data are presented in Table 3.5.1-5 :

Table 3.5.1-5. Incidence of Gross Masses in the lungs

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Percentage of Males Examined that Exhibited Lung Masses	Percentage of Females Examined that Exhibited Lung Masses
I	0	38%	17%
II	75	41%	48%*
III	150	53%	42%
IV	300	41%	50%*

*Indicates statistical significance at $p<0.05$.

No other remarkable gross pathology data were presented.

Histopathology/Tumor rates. Treatment of CD-1 mice resulted in an apparent increase in the incidence of pulmonary adenomas at all dosages that were studied and in both males and females; however, the differences were not statistically significant for a common tumor (p-values ≥ 0.005 for the trend test and ≥ 0.01 for pair-wise comparisons). The data are summarized below:

Table 3.5.1-6. Incidence of Pulmonary Adenomas

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Number of Males that Exhibited Pulmonary Adenomas (out of 52 examined)	Number of Females that Exhibited Pulmonary Adenomas (out of 52 examined)
I	0	11	6
II	75	18	11
III	150	16	17
IV	300	20	15

These data are included here because it appears that the differences might have achieved statistical significance if the group sizes had been larger. However, these data will not be discussed in the label of the product. Please see the Biostatistics review for discussion of the statistical methods that were used in the analysis of the data.

Conclusions. No statistically significant differences in tumor incidence were apparent in either male or female mice. This study appears to have been a valid carcinogenicity bioassay in all respects.

3.5.2. AF102B oncogenicity study by dietary administration to F-344 rats for 104 weeks, study No. —006/982306, in-life 8/95-9/97, study report dated 7/7/98, conducted by ——— in compliance with —— Good Laboratory Practice regulations.

This study involved 4 groups (dosage levels) of F-344 rats ———, each group initially containing 50 males and 50 females. The animals consumed feed that contained cevimeline HCl, resulting in approximate dosages of 0 (controls), 25, 50, or 100mg/Kg/day, 7 days per week for 104 weeks. These dosages were recommended by the exec. CAC following review of dose-ranging data (exec. CAC report dated 6/13/95). An additional 25 animals of each gender were maintained on feed at each of the three treatment groups (25, 50, or 100mg/Kg/day) for the purpose of toxicokinetic analysis; blood samples were obtained from 5 of these animals of each gender at 4 to 6 hour intervals (5 time points during a selected day) following 13, 26, and 52 weeks of exposure. The dietary concentrations of cevimeline HCl were adjusted on the basis of body weight and food consumption data to provide the estimated dosage; fresh food was prepared weekly for the first 14 weeks and every 2 weeks thereafter. Appropriate analyses of the feed were performed to ensure that the concentration and stability of cevimeline in the feed were suitable. In Table 3.5.2-1, the dosages of cevimeline used in this study are compared to the maximum dosage of cevimeline recommended (for a 60Kg individual) in the draft label of the product -mg/Kg/day).

Table 3.5.2-1. Dosage Comparisons Based on an Assumed Clinical Exposure to Cevimeline HCl of -mg/kg/day

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Multiple of Human Dose (Based on Body Weight)	Multiple of Human Dose (Based on Body Surface Area)	Multiple of Human Dose, Male Rats (Based on $AUC_{0-\infty}$)*	Multiple of Human Dose, Female Rats (Based on $AUC_{0-\infty}$)*
I	0	0	0	0	0
II	25	8	1	0.5	1
III	50	20	3	1	2
IV	100	30	5	3	4

*$AUC_{0-\infty}$ for a patient at the maximum proposed dosage is approximately 2000ng•hr/mL. Values are based on the AUC data presented in Table 3.5.2-3, below.

The parameters that were monitored included survival, clinical observations, body weight, food consumption, blood chemistry, hematology (including leukocyte differential), gross pathology,

and organ weights. Histopathology was performed on the following tissues:

Adrenals (cortex and medulla)
Aorta
Brain
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes and optic nerve
Femoral bone and marrow
Heart
Ileum
Jejunum
Kidneys
Liver
Lungs with bronchi
Lymph nodes (mandibular and mesenteric)
Mammary gland
Ovaries
Pancreas
Pituitary
Prostate
Salivary gland (submandibular)
Sciatic nerve
Seminal vesicles
Skeletal muscle
Skin
Smooth muscle
Spinal cord
Spleen
Sternum
Stomach
Testes
Thymus
Thyroid (with parathyroids)
Tongue
Trachea
Urinary bladder
Uterus with cervix
Vagina

And any gross lesions. Histopathology was performed on these tissues from all animals in groups I and IV (control and high-dose) and from animals found dead or sacrificed prematurely. In addition, the adrenals, pancreas, submandibular salivary gland, gross lesions, and "target organs" (organs in which lesions were observed in high-dose animals (lungs, ovaries, and uterus)) were histologically examined from group II and III animals.

Results.

Actual mean exposure levels. Based on body weight and food consumption data, the mean intakes of cevimeline HCl for the four groups were estimated; these data are presented in Table 3.5.2-2.

Table 3.5.2-2. Mean Dosages Actually Achieved (mg/Kg/day)

Group	Theoretical Dosage		Actual Mean Dosage	
	Males	Females	Males	Females
I	0	0	0	0
II	25	25	25.0	25.1
III	50	50	49.9	50.1
IV	100	100	99.8	100.1

Toxicokinetic data. AUC values calculated from samples obtained during week 52 are indicated in Table 3.5.2-3; similar values were obtained during weeks 13 and 26. Exposure increased roughly in proportion to dosage, with females experiencing a greater level of exposure at a given dosage.

Table 3.5.2-3. AUC Values from Week 52

Group	AUC (ng•h/mL)	
	Males	Females
I	NA	NA
II	934	1584
III	2070	3909
IV	5197	8350

Survival. The survival data for the animals designated to complete 104 weeks of exposure are presented in Table 3.5.2-4.

Table 3.5.2-4. Survival Rates of Rats at Terminal Sacrifice

Group	Dosage of Cevimeline HCl (mg/Kg/day)	Number of Males that Survived to the Scheduled Sacrifice	Number of Females that Survived to the Scheduled Sacrifice
I	0	34	33
II	25	39	43
III	50	40	44
IV	100	34	40

None of the groups exhibited a treatment-related decrease in survival.

Clinical observations. Observations that were considered to be related to treatment included "thin build" (females at 50mg/Kg/day and above and males at 100mg/Kg/day); "ungroomed

coat" (both males and females at 100mg/Kg/day); and "urine stained fur" (males only at 100mg/Kg/day).

Body weight. Mean body weight and mean body weight gain were reduced in a dose-dependent manner in both males and females; statistically significant differences were observed in both genders at 50mg/Kg/day and above.

Food consumption. Mean food consumption was reduced in a dose-dependent manner in both males and females (ranging from approximately 5 to 15% of the control value).

Clinical pathology. A dosage-related decrease in plasma cholesterol was observed in both males and females. A few other anomalous clinical pathological values were obtained, but the meaning of these findings in two-year old rats is unclear.

Organ weights. Although a number of statistically significant differences in the mean absolute and normalized-to-body-weight values of certain organs were observed, the organ weight data do not suggest treatment-related effects.

Gross pathology. No remarkable observations.

Histopathology/Tumor rates. No statistically significant differences or trends in the incidence of tumors were observed in male rats. In females, the incidence of adenocarcinomas of the uterus in the high-dose group was statistically significantly increased; the data are summarized below:

Table 3.5.2-5. Incidence of Uterine Adenocarcinomas

Group	Theoretical Dosage of Cevimeline HCl (mg/Kg/day)	Number of Adenocarcinomas of the Uterus Observed
I	0	0
II	25	1°
III	50	0
IV	100	4*

°Two uterine adenomas also observed in this group.
*P values: Trend test = 0.007, Pair-wise (group I vs. group IV) = 0.033

Historical control data supplied by the contracting laboratory indicate that uterine adenocarcinomas have been observed in approximately 2% of the control females in studies involving two-year assays in F344 rats conducted by ——— in the recent past (range 0/60 to 2/60). The incidence in the high-dose group in the current study was 8%. Note: The historic data were obtained from animals purchased from ——— while the study reviewed here utilized rats obtained from ———

[redacted] It is assumed that the incidence of spontaneous adenocarcinomas of the uterus in this strain of rat does not vary between these two sources. No significant differences or trends were observed in the incidence of uterine sarcomas, uterine adenomas, or uterine stromal polyps, or any combined values. Only two uterine adenomas were reported in the study, and both were in the low-dose group. The p-values (trend and pair-wise comparison for high-dose vs. control) for the combined incidence of uterine adenomas and adenocarcinomas were 0.049 and 0.033, respectively.

Please see the Biostatistics review for discussion of the statistical methods that were used in the analysis of these data.

Conclusions. Exposure to cevimeline may have increased the incidence of adenocarcinomas of the uterus in female F-344 rats. No other effects upon tumor incidence were apparent in either male or female rats. This study appears to have been a valid carcinogenicity bioassay in all respects.

Summary: Cevimeline is an agonist of muscarinic cholinergic receptors. It elicits the actions characteristic of drugs of this class, including salivation, lacrimation, and, at sufficient dosage, diarrhea and tremor. Cevimeline was rapidly and almost completely absorbed following oral dosing of rats and dogs, with a T_{max} of 30 to 60 minutes. Cevimeline is cleared almost exclusively through the urine, predominantly as a trans-sulfoxide metabolite. The elimination half-life was estimated to be one to two hours.

The oral LD_{50} of cevimeline in rats is approximately 110mg/kg. In a one-year repeat dose toxicology study in rats, animals at 36mg/kg/day (high-dose group) exhibited mydriasis, salivation, lacrimation, soft stools, clonic/tonic convulsions, "standing on tiptoe", dyspnea, and perigenital staining, increased mean weight of the salivary and adrenal glands, a trend toward increased mean liver weight, increased mean kidney weight (latter effect in females only), and hypertrophy of the acinar cells of the salivary glands and pancreas. Slightly increased mean pancreatic weight was observed at all dosages studied, and therefore a NOAEL (NO-Adverse-Effect-Level) was not observed in the study, although for practical purposes the mid-dose (6mg/kg/day) can be regarded as being a NOAEL. Similar results were obtained in a one-year repeat dose toxicology study in dogs, in which animals at 18mg/kg/day (high-dose group) exhibited signs of excessive cholinergic stimulation (e.g., salivation, diarrhea, lacrimation, and tremor), as expected for a cholinomemetic drug, but no apparent adverse effects were observed that were not secondary to the pharmacodynamic properties of the drug substance.

Cevimeline did not adversely effect the reproductive performance or fertility of rats when administered prior to mating through day seven of gestation, although animals in the high-dose group (45mg/kg/day) exhibited a reduction in the mean number of implantations, and a higher number of visceral anomalies in F1 animals (first-generation offspring). In that ("Segment 1") study, the percentage of fetuses with skeletal variations increased in proportion to dosage. However, it is unlikely that these effects would be apparent at clinical dosages. No developmental effects were observed in teratology studies in rats and rabbits. When administered during the last three days of pregnancy and throughout the period of lactation ("Segment 3" or perinatal development study), cevimeline apparently caused no substantial adverse effects on reproduction or developmental parameters, with the exception that F1 animals associated with the high-dose (45mg/kg/day) group exhibited mean body weights that were statistically significantly lower than control F1 animals from day 0 through day 42 postpartum. This effect was reversible, and the mean pup weights did not differ from control values after day 42.

Cevimeline is apparently not a genetic toxicant; negative results were obtained in an Ames test, a chromosomal aberration

study in cultured fibroblasts, a mouse lymphoma study in L5178Y cells, or in a micronucleus assay.

Cevimeline was assessed for carcinogenicity in two-year bioassays in CD-1 mice and F-344 rats. Among female rats, the incidence of uterine adenocarcinomas in animals that received 100mg/kg/day cevimeline HCl was significantly greater than in control animals. No other statistically significant differences in tumor incidence were observed in either species.

Labeling: The following changes in the label are recommended:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility section:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100mg/kg/day (approximately — times the maximum human exposure based on comparison of AUC data). No other significant differences in tumor incidence were observed in either mice or rats.

Cevimeline exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an *in vitro* chromosomal aberration study in mammalian cells, a mouse lymphoma study in L5178Y cells, or in a micronucleus assay conducted *in vivo* in ICR mice.

Cevimeline did not adversely effect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45mg/kg/day (approximately — times the maximum recommended dose for a 50kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at dosages up to 45mg/kg/day from 14 days prior to mating through day seven of gestation exhibited a statistically significantly smaller number of implantations than did control animals.

2. Pregnancy Category:

Pregnancy:
Pregnancy Category C. Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately — times the maximum recommended dose for a 50kg human when compared on the basis of body surface area estimates). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Evaluation and recommendations: This NDA is approvable with respect to pharmacologic and toxicologic concerns. Recommended modifications of the labeling are indicated above.

/S/ 5/24/99

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 20-989
HFD-540 Div. File
HFD-540/TL/JACOBS
HFD-540/PHARM/SEE
HFD-540/MO/HYMAN
HFD-540/CHEM/VIDRA
HFD-540/CSO/BLAY
HFD-345

Concurrence Only:
HFD-540/DD/WILKIN /S/ 7/9/99
HFD-540/TL/JACOBS /S/ 5/24/99

APPEARS THIS WAY
ON ORIGINAL

NDA 20-989

Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

DEC 23 1999

Norman A. See, Ph.D., R.Ph.
Draft Completed: 12/22/99

Amendment BP
Submission Date: 12/13/99
Center Receipt Date: 12/14/99

Sponsor: Snow Brand Pharmaceuticals, Inc.

Drug: Cevimeline HCl; Evoxac Capsules

Formulation: Oral Capsules, 30mg

Proposed Indication: Xerostomia in patients with Sjogren's syndrome.

Related Drugs/INDs/NDAs: IND ———

Background: The original submission to NDA 20-989 proposed marketing of 30mg ——— capsules of cevimeline HCl, both labeled for ingestion up to three times daily. Previous pharmacology reviews of the draft label for Evoxac included "dose-multiples" (comparisons of the nonclinical and clinical exposures) that were based upon a maximum clinical dosage of ——— three times daily. However, it has recently come to my attention that the clinical reviewer has found that the ——— dosage, three times daily, offered no benefit over the 30mg dosage, three times daily, and the proposal to market the ——— form has been withdrawn. Therefore, the maximum clinical dose has been ——— necessitating recalculation of the dose-multiples. The purpose of this review is to revise the language for the portions of the product label that discuss nonclinical studies such that the stated dose-multiples will be based upon a clinical dose of 30mg three times daily. As stated in a previous labeling review (Pharmacology review dated 12/1/99), I recommend that the third sentence of the first paragraph of the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section (as submitted in the amendment of 11/11/99) be removed; that sentence reads: ——— The sponsor's proposed label, as submitted in the amendment of 11/11/99, is otherwise acceptable with respect to nonclinical issues.

Labeling Review: The following changes in the label are recommended (deletions are indicated by strike-through; inserted new text is indicated by underline):

1. Carcinogenesis, Mutagenesis, Impairment of Fertility section:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100mg/kg/day (approximately ~ 8 times the maximum human exposure based on comparison of AUC data). No other significant differences in tumor incidence were observed in either mice or rats.

Cevimeline exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an *in vitro* chromosomal aberration study in mammalian cells, a mouse lymphoma study in L5178Y cells, or in a micronucleus assay conducted *in vivo* in ICR mice.

Cevimeline did not adversely effect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45mg/kg/day (approximately ~ 5 times the maximum recommended dose for a 60kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at dosages up to 45mg/kg/day from 14 days prior to mating through day seven of gestation exhibited a statistically significantly smaller number of implantations than did control animals.

2. Pregnancy Category:

Pregnancy:
Pregnancy Category C. Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately ~ 5 times the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

With those changes made, these sections would read:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100mg/kg/day (approximately 8 times the maximum human exposure based on comparison of AUC data). No other significant differences in tumor incidence were observed in either mice or rats.

Cevimeline exhibited no evidence of mutagenicity or clastogenicity in a battery of assays that included an Ames test, an *in vitro* chromosomal aberration study in mammalian cells, a mouse lymphoma study in L5178Y cells, or in a micronucleus assay conducted *in vivo* in ICR mice.

Cevimeline did not adversely effect the reproductive performance or fertility of male Sprague-Dawley rats when administered for 63 days prior to mating and throughout the period of mating at dosages up to 45mg/kg/day (approximately 5 times the maximum recommended dose for a 60kg human following normalization of the data on the basis of body surface area estimates). Females that were treated with cevimeline at dosages up to 45mg/kg/day from 14 days prior to mating through day seven of gestation exhibited a statistically significantly smaller number of implantations than did control animals.

Pregnancy:

Pregnancy Category C. Cevimeline was associated with a reduction in the mean number of implantations when given to pregnant Sprague-Dawley rats from 14 days prior to mating through day seven of gestation at a dosage of 45mg/kg/day (approximately 5 times the maximum recommended dose for a 60kg human when compared on the basis of body surface area estimates). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Cevimeline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Evaluation and recommendations: This NDA is approvable with respect to pharmacologic and toxicologic concerns. Recommended modifications of the labeling are indicated above.

APPEARS THIS WAY
ON ORIGINAL

/S/

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 20-989
HFD-540 Div. File
HFD-540/TL/JACOBS
HFD-540/PHARM/SEE
HFD-540/MO/HYMAN
HFD-540/CHEM/VIDRA
HFD-540/CSO/CINTRON

Concurrence Only:
HFD-540/DD/WILKIN /S/ 12/30/99
HFD-540/TL/JACOBS /S/ 12/30/99 ✓ DFS

NDA 20-989

Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

DEC 1 1999

Norman A. See, Ph.D., R.Ph.
Draft Completed: 12/1/99

Amendment AZ
Submission Date: 11/11/99
Center Receipt Date: 11/12/99

Sponsor: Snow Brand Pharmaceuticals, Inc.

Drug: Cevimeline HCl; Evoxac Capsules

Formulation: Oral Capsules, 30mg

Proposed Indication: Xerostomia in patients with Sjogren's syndrome.

Related Drugs/INDs/NDAs: IND

Background: This amendment contained a revised draft label for Evoxac.

Labeling: I recommend that the third sentence of the first paragraph of the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section be removed; that sentence reads:

Although technically correct, that statement could be made concerning virtually any finding from a nonclinical study. It is not CDER policy to include in product labels observation of the fact that

The revised "Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the label, with the indicated sentence omitted, would then read:

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Lifetime carcinogenicity studies were conducted in CD-1 mice and F-344 rats. A statistically significant increase in the incidence of adenocarcinomas of the uterus was observed in female rats that received cevimeline at a dosage of 100mg/kg/day (approximately – times the maximum human exposure based on comparison of AUC

data). No other significant differences in tumor incidence were observed in either mice or rats.

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The sponsor's proposed label, as submitted in the amendment of 11/11/99, is otherwise acceptable with respect to nonclinical issues.

Evaluation and recommendations: This NDA is approvable with respect to pharmacologic and toxicologic concerns. Recommended modifications of the labeling are indicated above.

APPEARS THIS WAY
ON ORIGINAL

12/1/99

/S/

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 20-989
HFD-540 Div. File
HFD-540/TL/JACOBS
HFD-540/PHARM/SEE
HFD-540/MO/HYMAN
HFD-540/CHEM/VIDRA
HFD-540/CSO/CINTRON

Concurrence Only:
HFD-540/DD/WILKIN /S/ 12/2/99
HFD-540/TL/JACOBS /S/ 12/1/99

not found in DFS

faDFS