CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-237/S-007

PHARMACOLOGY REVIEW(S)

HFD 540/Dia

NDA 20-237

APR 25 1997

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

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Supplement 007
Submission Date: 2/11/97
Center Receipt Date: 2/12/97

Sponsor: MGI Pharma, Inc.

Drug: Salagen®; pilocarpine HCl

Pharmacological Category: Direct-acting non-selective muscarinic agonist.

Formulation: 5mg tablets

Proposed Indication: Xerostomia secondary to radiation or Sjogren's syndrome

Related Drugs/INDs/NDAs: IND

Background Information: On 11/13/91, HFD-160, in conjunction with office-level personnel, made an agreement with MGI Pharma, Inc., that approval of a NDA for oral pilocarpine HCl would require carcinogenicity bioassay data from only one species (the rat), and that these data could be submitted post-approval of the NDA. The NDA (20-237; Salagen®) has since been filed and was approved on 3/22/94. The approved indication for Salagen® is "the treatment of symptoms of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck". The limited patient population (i.e., individuals with a history of cancer) was a primary factor in the decision to require limited carcinogenicity data. It was believed that these individuals (relative to the general population) would have a fairly high probability of developing cancer either as a recurrence of their previous disease or as a result of prior exposure to radiation and other carcinogenic (chemotherapeutic) agents. Therefore, it was decided that the additional risk that might be posed by a drug substance that had not been completely characterized as a potential carcinogen was adequately counter balanced in these patients by the potential therapeutic benefits to be derived from reduced xerostomia.

MGI Pharma, Inc., recently submitted an efficacy supplement (S-007) to NDA 20-237 that proposes modification of the label to include Sjogren's syndrome as an approved indication. Sjogren's syndrome is a chronic, slowly progressive autoimmune disorder, characterized by lymphocytic infiltration of the exocrine glands, that results in hyposalivation and hypolacrimation. The patient population that is afflicted with Sjogren's syndrome includes otherwise healthy individuals of all ages, including children. The incidence of the disease is unknown, but is thought to be fairly high, since, in addition to patients with primary Sjogren's syndrome, it is estimated that 30 percent of patients with rheumatoid arthritis, systemic lupus erythematosus, and scleroderma suffer from "secondary" Sjogren's syndrome[1]. Since the product would no longer be limited to use in patients with a history of cancer and exposure to carcinogens, and would be used on a chronic basis, labeling for Sjogren's syndrome as an approved indication would require support from carcinogenicity data obtained from two species to be consistent with CDER policy.

It was agreed in a meeting on 10/11/96 between MGI Pharma and division personnel that carcinogenicity data from a second species would be regarded as a phase 4 commitment to an efficacy supplement for Sjogren's syndrome. The sponsor agreed to include in the supplement the final draft of a 13 week dose-ranging study and a protocol for the second-species bioassay. Those documents, together with some toxicology studies conducted in dogs, were submitted in S-007 and are reviewed below. The mouse bioassay has already been initiated and is being conducted by a Japanese affiliate of MGI Pharma, Inc. The protocol was not evaluated by division personnel prior to initiation, and will not be evaluated by the executive carcinogenicity assessment committee of CDER. MGI Pharma will have access to the final report of the bioassay and plans to submit that report in support of NDA 20-237. The dog studies were performed pursuant to Japanese regulatory requirements, and were included in the supplement in the interest of full disclosure of safety information.

Studies/protocols Submitted in supplement 007:

1. 13-week mouse subchronic toxicology study (dose-ranging study for bioassay).

2. Protocol for mouse carcinogenicity bioassay.

3. Acute dog toxicology study.

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[1]Harrison's Principles of Internal Medicine, 13th ed., McGraw-Hill, Inc, 1994.

4. 14-day dog toxicology study.

5. 28-day dog toxicology study.

6. 26-week dog toxicology study.

Review of Nonclinical Information Supporting the Safety of the Proposed Change in the Label of Salagen:

1. KSS-694: Toxicity study in mice by oral administration for 13 weeks, study No. KSI 60/961456, in-life 12/95-4/96, report not signed or dated, conducted by , in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

Approximately 6-week old CD-1 BR mice were randomly assigned into treatment groups as indicated below:

	Dose (mg/kg)	Number of Animals Male	Female
Main study Animals			
Control	0	10	10
Low-dose	10	10	10
Mid-dose	30	10	10
High-dose	90	10	10
Toxicokinetic Animals			
Low-dose	10	21	21
Mid-dose	30	21	21
High-dose	90	21	21

The animals were dosed once daily by gavage, 7 days per week for 13 weeks. The dose volume for all animals was 5ml/kg. Water was used as a vehicle. The batch number of the test article (pilocarpine HCl) was 462320. Food and water were available *ad libitum*. The dosages used in this study are compared to the maximum proposed clinical dosage (30mg/day, or 0.6mg/kg/day in a 50kg individual; clinical AUC_{0-24} is approx. 108ng·h/mL) below:

Mouse dose (mg/kg/day)	Multiple of human dose (mg/kg)	Multiple of human dose (mg/m²)	Approx. AUC ratio
10	17	1.5	20
30	50	4	80
90	150	13	300

Main study animals: The parameters that were monitored were survival, clinical signs, body weight, food and water consumption, gross necropsy, organ weights, and histopathology of

macroscopically abnormal tissues.

Toxicokinetic animals: Blood samples were collected from 3 animals per sex from each toxicokinetic group on the last day of treatment at 0, 0.25, 0.5, 1, 2, 4, and 24 hours after dosing. The concentration of pilocarpine in the plasma was determined for each sample, and the data were used to calculate the C_{max}, T_{max}, and the AUC_{0-24}.

Results.

1. Toxicology data.

Mortalities. Nine unscheduled deaths occurred, five among the "main study" groups and four among the "toxicokinetic" groups. All of the animals that died early were males, one at 10mg/kg/day, four at 30mg/kg/day, and four at 90mg/kg/day. At least two of the deaths were apparently not related to treatment. No information was provided concerning the causes of the other deaths.

Clinical signs. Salivation, wet coats, lethargy, and watery discharge from the eyes were observed at 90mg/kg/day and to a lesser extent at 30mg/kg/day. 10mg/kg/day was a NOAEL for adverse clinical signs.

Body weight. A trend toward reduced mean body weight gain was observed in both male and female animals; the reduction achieved statistical significance at 30mg/kg/day and above.

Food consumption. No remarkable effects.

Organ weights. The following observations were made:

Males: Statistically significantly reduced means of the absolute thymus weight were observed at 30mg/kg/day and above. Trends toward reduced means of the absolute liver weight were observed, and the differences became statistically significant at all treatment levels following normalization of the data to body weight. Trends toward increased means of the absolute weight of submaxillary salivary glands were observed, and the differences became statistically significant at 30mg/kg/day and above following normalization of the data to body weight.

Females: Trends toward increased means of the absolute kidney weight were observed, and the differences became statistically significant at 30mg/kg/day and above following normalization of the data to body weight. Trends toward increased means of the absolute weight of submaxillary salivary glands were observed, and the differences became statistically significant at all treatment levels following normalization of the data to body weight.

No other remarkable effects on organ weight were observed in either male or female animals.

Gross necropsy. Reduced size of the thymus was observed in some high-dose males, which correlated with reduced mean absolute weight of the thymus. Reductions in the quantity of adipose tissue were observed in high-dose males and females, which correlated with the reduced mean body weight gain. An increased incidence of alopecia was observed in high-dose males. No other remarkable effects were reported.

Histopathology. No remarkable observations, but histopathology was limited to macroscopically abnormal tissues.

Toxicokinetic evaluation. The maximum plasma concentration (C_{max}) and AUC of pilocarpine increased in an approximately linear manner over the dosage range that was studied:

Dosage (mg/kg/day)	C_{max} (ng/mL)		T_{max} (hrs.)		AUC_{0-t} (ng·h/mL)	
	Males	Females	Males	Females	Males	Females
10	4180	2871	0.25	0.25	2547	2190
30	10506	15101	0.25	0.25	8504	11499
90	34939	24989	0.25	0.25	32521	33529

Summary and reviewer's comments concerning the Dose-Ranging Study: Toxicity was observed at 30mg/kg/day and above, including decreased survival, adverse clinical signs, reduced weight gain, and altered mean organ weights. A dose of 10mg/kg/day was a NOAEL with regard to statistically significant deviations from control values, although animals that received 10mg/kg/day exhibited trends toward some effects (e.g., reduced weight gain, reduced mean liver weight in males) that became statistically significant at higher dosages. These effects (differences) would probably have been statistically significant if the group sizes had been larger, and it is possible that 10mg/kg/day may exceed the MTD for an 80 week study. It is difficult to estimate the MTD from these data, but the dosages selected for the 80 week bioassay (3, 10, and 30mg/kg/day) appear to be at least adequately high, both in terms of toxicity (MTD approach) and exposure (mouse:human AUC ratios of approximately 20 and 80 should be yielded by the mid and high dosages, respectively). The dosage selection is deemed acceptable, provided survival is adequate.

2. Review of the Protocol for a Mouse Bioassay:

KSS-694: Potential tumorigenic effects by oral administration to mice (according to Japanese MOHW guidelines), currently being conducted by
in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

The study, currently underway, is utilizing :CD-1 BR mice. Shortly after arrival, 5 animals of each sex were selected for a "baseline health screen", which consisted of macroscopic examination and histopathological examination of any gross lesions. The remaining animals were randomly assigned into treatment groups as indicated below:

	Proposed Dose (mg/kg)	Number of Animals Male	Female
Carcinogenicity Animals			
Control group	0	56	56
Low-dose	3	56	56
Mid-dose	10	56	56
High-dose	30	56	56
Toxicokinetic Animals			
Low-dose	3	28	28
Mid-dose	10	28	28
High-dose	30	28	28

The animals were apparently approximately 40 days old at initiation of treatment. The animals are being housed by sex in groups of two. A commercial rodent feed and water are available *ad libitum*. The animals are being dosed once daily by gavage (5ml/kg), 7 days per week, for 80 weeks. The test material is dissolved in water and the test solutions are stored at 20°C and used within 7 days of preparation.

Observations:

Carcinogenicity Animals. The animals will be examined daily for abnormal clinical signs and at least once weekly for palpable masses. Additional parameters that will be monitored include body weight (weekly), food consumption (per cage), hematology (at sacrifice, including WBC differential), gross necropsy, and histopathology of control and high-dose animals. Any tissues that exhibit a treatment-related histopathological effect in high-dose animals will also be histopathologically examined from low and mid-dose animals. Tissues to be subjected to histopathology include:

Adrenals

Brain
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes
Femur (with joint)
Heart
Ileum
Jejunum
Kidneys
Liver
Lungs
Lymph Nodes (Mesenteric and Cervical)
Mammary Gland
Ovaries
Pancreas
Pituitary
Prostate
Rectum
Salivary Gland
Seminal Vesicles
Skin
Spinal Cord
Spleen
Sternum (incl. marrow)
Stomach
Testes
Thymus
Thyroid (with parathyroid)
Tongue
Trachea
Urinary Bladder
Uterus
Vagina

And all gross lesions.

Toxicokinetic Animals. Blood samples will be obtained for determination of the plasma concentration of the test article. Four animals per sex per group will be sampled at 0.25 and 24 hours after dosing during months 3, 12, and 18 of dosing. These time points were estimated to be the T_{max} and T_{min}, respectively, based on data obtained during the dose-ranging study.

Reviewer's Comments and Recommendations Concerning the Protocol for the Carcinogenicity Assay: The protocol is acceptable to the division. It would have been preferable for the study to have been of greater duration (104 weeks, with a provision for early

termination if excessive mortality occurred), and the list of tissues that will be subjected to histopathology should have included the gall bladder, Harderian gland, and the zymbal gland. Preferably, blood samples should be obtained for toxicokinetic purposes at at least three time points that are within a few hours of the anticipated T_{max} (0.25 hours). However, the toxicokinetic data obtained in the dose-ranging study, which involved 7 time points, should be adequate, and the other flaws in the protocol are not serious enough to invalidate the study. It is difficult to estimate the MTD from the data obtained in the dose-ranging study, but the dosages selected for the 80 week bioassay (3, 10, and 30mg/kg/day) appear to be at least adequately high, both in terms of toxicity (MTD approach) and exposure (mouse:human AUC ratios of approximately 20 and 80 should be yielded by the mid and high dosages, respectively). The dosage selection is deemed acceptable, provided survival is adequate.

3. KSS-694: Acute toxicity study by oral (capsule) administration to male beagle dogs, study No. 95/KST006/0393, in-life 10/94-12/94, report dated 4/13/95, conducted by in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

Four male beagles were fasted overnight. Each dog then received a gelatin capsule that contained pilocarpine (lot No. 462320, stated to be 100% pure); 2 dogs received 25mg/kg and 2 received 50mg/kg. The dogs were monitored for 16 days after dosing. The parameters that were monitored included clinical signs, survival, bodyweight, food consumption, physical examination, hematology, blood chemistry, urinalysis, fecal blood, necropsy, and organ weights.

Results.

Survival. No deaths at 25mg/kg. One dog at 50mg/kg was sacrificed 7 hours after dosing due to signs of suffering (respiratory distress, vomiting, prone position).

Clinical signs. Signs of toxicity were observed beginning about 15 minutes after dosing, were proportional to dosage, and included vomiting, ataxia, marked salivation, hypoactivity, blood in the feces, labored and noisy breathing, pale gums, hunched posture, dilated pupils, reduced body temperature, prone posture, watery discharge from the eyes, splayed hindlimbs, and body tremors. Note that these are the characteristic signs of intoxication with a cholinomimetic agent. These signs had largely disappeared within 6 to 24 hours post-dosing, although the surviving high-dose animal was slightly ataxic until day 3.

Other effects. No other remarkable observations were made of the

3 dogs that survived to scheduled sacrifice. The animal sacrificed prematurely exhibited dehydration, elevated serum enzyme activities, increased lung weight (pulmonary edema), and dark lungs and lymph nodes.

Conclusion. A single dose of 50mg/kg caused one fatality and clearly exceeded the maximum-tolerated-dose under the conditions of this study. A single dose of 25mg/kg caused signs of toxicity but was considered to be suitable as the high-dose in a 14-day repeat-dose study (see below).

4. KSS-694: Preliminary toxicity study by oral (capsule) administration to beagle dogs for two weeks, study No. 95/KST007/0240, in-life 10/94-1/95, report dated 5/31/95, conducted by in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

This was a preliminary study, conducted to determine the dosages to be used in a 28-day study. Three groups of dogs (1 beagle/sex/group) received pilocarpine (lot No. 462320) at dosages of either 3, 8, or 25mg/kg/day for 14 consecutive days. The parameters that were monitored included clinical signs, survival, bodyweight, food consumption, physical examination, hematology, blood chemistry, urinalysis, fecal blood, necropsy, organ weights, and histopathology of gross lesions (only).

Results.

Survival. No unscheduled deaths.

Clinical signs. Signs of toxicity were observed within 1 or 2 hours after dosing, continued throughout the study (observed after each dose), were proportional to dosage, and included vomiting, salivation, hypoactivity, coughing, diarrhea, dry nose, slow heart rate, and body tremors.

Bodyweight. No remarkable effects.

Hematology. Both animals at 25mg/kg/day exhibited a high-platelet count. No clear effects were observed at 8mg/kg/day or below.

Blood chemistry. Both animals at 25mg/kg/day exhibited elevated serum enzyme activities. No clear effects were observed at 8mg/kg/day or below.

Urinalysis. Urinalysis on days 11 and 12 indicated low electrolyte output at all dosage levels.

Organ weights. The male at 25mg/kg/day exhibited reduced spleen

weight and increased liver weight (compared to the other treated males and to historical values). No remarkable effects were observed on mean organ weight at 8mg/kg/day or below.

Conclusion. A dosage of 25mg/kg/day for 14 days caused abnormal clinical signs and changes in hematology and blood chemistry. Dosages of 3 and 8mg/kg/day were considered to have been well tolerated.

5. KSS-694: Toxicity study by oral (capsule) administration to beagle dogs for four weeks followed by a four week reversibility period, study No. 95/KST008/0769, in-life 1/95-4/95, report dated 10/27/95, conducted by , in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

Four groups of dogs (4 beagles/sex/group) received pilocarpine (lot No. 462320) at initial dosages of either 0 (controls), 1, 5, or 25mg/kg/day. However, dosing was discontinued in the high-dose group after 4 days due to excessive toxicity. Surviving "high-dose" animals were maintained without treatment for 24 days and then treated at 0.5mg/kg/day for 28 consecutive days. Animals at 0, 1, and 5mg/kg/day were treated for 28 consecutive days. At the conclusion of the treatment period 3 animals of each gender from each group were sacrificed. The remaining 1 dog/sex/group was maintained without treatment for 4 weeks (allowed to recover from treatment) prior to sacrifice. The parameters that were monitored included clinical signs, survival, bodyweight, food consumption, physical examination, ophthalmology, ECG, hematology, blood chemistry, urinalysis, necropsy, organ weights, and histopathology of major tissues from all animals. Blood samples were obtained from each animal on days 1 and 27 of treatment at 1, 3, 6, and 24 hours post-dosing for limited toxicokinetic analysis.

Results.

Survival. One female and 1 male at 25mg/kg/day were sacrificed (on days 4 and 5, respectively) due to intestinal trauma. No other unscheduled deaths occurred.

Clinical signs. Signs of toxicity were observed approximately 30 minutes after dosing, continued throughout the study (observed after each dose), were proportional to dosage, disappeared during the reversibility period, and included vomiting, salivation, hypoactivity, coughing, diarrhea, dry nose, and body tremors.

Bodyweight. No remarkable effects.

Food consumption. No remarkable effects.

Ophthalmology. No remarkable effects.

ECG. No remarkable effects (not done on animals at 25mg/kg/day).

Hematology. No remarkable effects (not done on animals at 25mg/kg/day).

Blood chemistry. Slight electrolyte imbalances were observed in males and females at 5mg/kg/day. No remarkable effects at 0.5 or 1mg/kg/day.

Urinalysis. Low electrolyte output at 5mg/kg/day. No remarkable effects at 0.5 or 1mg/kg/day.

Organ weights. Increased mean weight of the submandibular salivary gland at 5mg/kg/day; no remarkable effects at 0.5 or 1mg/kg/day.

Gross pathology (necropsy). No remarkable effects.

Histopathology. Animals at 5mg/kg/day exhibited hypertrophy of the submandibular salivary glands and the submucosal glands of the esophagus. No remarkable effects at 0.5 or 1mg/kg/day.

Toxicokinetics. The plasma level data were inadequate to permit proper toxicokinetic analysis because C_{max} was observed at the first time point (1 hour), making accurate assessment of the AUC impossible (the true C_{max} may have occurred at a substantially earlier time point, e.g., 15 minutes post-dosing). The plasma level at 1 hour post-dosing increased in proportion to dose; the level was generally below the limit of detection by 6 hours post-dosing.

Conclusion. A dosage of 0.5mg/kg/day was considered to be a NOAEL under the conditions of this study. Excessive toxicity was observed at 25mg/kg/day.

6. KSS-694: Toxicity study by oral capsule administration to beagle dogs for 26 weeks, study No. 96/KST010/0512, in-life 7/95-2/96, report dated 11/27/96, conducted by in compliance with OECD Good Laboratory Practice regulations.

Four groups of dogs (3 beagles/sex/group) received pilocarpine (lot No. 462320) at dosages of either 0 (controls), 0.5, 1, or 3mg/kg/day, 7 days per week, for 26 weeks. Recovery animals were not included in the study. The dosages used in this study are compared to the maximum proposed clinical dosage

(30mg/day, or 0.6mg/kg/day in a 50kg individual) below:

Dog dose (mg/kg/day)	Multiple of human dose (mg/kg)	Multiple of human dose (mg/m²)
0.5	0.83	0.49
1	1.7	0.98
3	5	2.9

The parameters that were monitored included clinical signs, survival, bodyweight, food consumption, physical examination, ophthalmology, ECG, hematology, blood chemistry, urinalysis, necropsy, organ weights, and histopathology of major tissues from all animals. Blood samples were obtained from each animal on day 1 and after 11 and 24 weeks of treatment at 1 and 24 hours post-dosing for limited toxicokinetic analysis.

Results.

Survival. No unscheduled deaths occurred.

Clinical signs.

At 3mg/kg/day: Vomiting, hypoactivity, dry nose, salivation, body tremors, clear discharge from eyes, coughing, diarrhea, a wet ventral coat, and fecal staining.

At 1mg/kg/day: Salivation, clear discharge from eyes, coughing, diarrhea, and a wet ventral coat.

At 0.5mg/kg/day: Salivation.

Bodyweight. Bodyweight gain was statistically significantly reduced in high-dose females (62% of control value). No remarkable effects in any other dosage/gender group.

Food consumption. No remarkable effects.

Ophthalmology. No structural changes of the eye. Animals at 3mg/kg/day exhibited conjunctivitis.

ECG. No remarkable effects.

Hematology. No remarkable effects.

Blood chemistry. No remarkable effects.

Urinalysis. Reduced volume and electrolyte output at 3mg/kg/day. No remarkable effects at 0.5 or 1mg/kg/day.

Organ weights. Increased mean weight of the adrenals (both genders), the submandibular salivary gland (both genders), the parotid salivary gland (females only), and the spleen (males

only) at 3mg/kg/day; no remarkable effects at 0.5 or 1mg/kg/day.

Gross pathology (necropsy). No remarkable effects.

Histopathology. Animals (both genders) at 3mg/kg/day exhibited hypertrophy of the adrenal cortices and acinar hyperplasia of the submandibular salivary glands. Changes in the epididymides of males at 3mg/kg/day included the presence of germ cells (all 3 dogs), hypospermia (2 of 3 dogs), and periductal chronic inflammation (2 of 3 dogs). Slight degeneration of the seminiferous epithelium in the testes was observed in 1 male at 3mg/kg/day, and a reduction in the number of maturation-phase spermatids was observed in another. One animal at 1mg/kg/day exhibited hypospermia and a sperm granuloma in the left epididymis; it was unclear if these effects at 1mg/kg/day were related to treatment. No remarkable effects at 0.5mg/kg/day.

Toxicokinetics. The plasma level data were inadequate to permit proper toxicokinetic analysis because blood samples were drawn at only one time point (1 hour) at which measurable levels of pilocarpine were present. The plasma level at 1 hour post-dosing increased in proportion to dose; the level was below the limit of detection by 24 hours post-dosing.

Conclusion. Toxicity was observed at 3mg/kg/day, including reduced body weight gain in females and effects on the epididymides and testes of males. The latter effects suggest an adverse effect on spermatogenesis. A dosage of 1mg/kg/day was considered to be a NOAEL under the conditions of this study, with the exception of clinical signs that are related to the pharmacological action of pilocarpine (salivation, etc.) and the possible exception of hypospermia in the left epididymis of one animal.

Regulatory Conclusion: The proposed expansion of the label of Salagen® to include Sjogren's syndrome as an approved indication is approvable in regard to pharmacologic and toxicologic concerns. However, it is recommended that the label of Salagen® also be modified to include discussion of the adverse effects that pilocarpine apparently had upon spermatogenesis in dogs that received pilocarpine for 26 weeks. Proposed changes in the product label are indicated below. It is recommended that the label changes be communicated to the sponsor.

Draft comments to the sponsor:

Please make the following modifications to the label of NDA 20-237 to incorporate the data contained in the submission dated 11-FEB-97 and to comply with 21 CFR 201.57:

3/17/97

/S/

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

cc:
NDA 20-237
Supp. No. 007
HFD-540 Div. File
HFD-540/TL/JACOBS
HFD-540/PHARM/SEE
HFD-540/CSO/BLATT
HFD-345

Concurrence Only:
HFD-540/DD/WILKIN 4/25/97
HFD-540/TL/JACOBS 3/17/97