

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-237/S-012

Trade Name: Salagen

Generic Name: pilocarpine hydrochloride

Sponsor: MGI Pharma

Approval Date: April 18, 2003

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APPLICATION NUMBER:

NDA 20-237/S-012

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APPLICATION NUMBER:

NDA 20-237/S-012

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-237

MGI Pharma
Attention: Winifred C. Wu, R.Ph.
Senior Director, Regulatory Affairs
5775 West Old Shakopee Road
Suite 100
Bloomington, MN 55437-3174

Dear Ms. Wu:

Please refer to your supplemental new drug application dated December 19, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Salagen (pilocarpine hydrochloride) tablets.

This supplemental new drug application provides for the manufacture and marketing of an additional strength (7.5 mg).

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please be reminded that the Agency requested revisions on your current labeling during the next printing. (See FDA's supplemental letter dated March 20, 2003, in response to the FPL submission of November 14, 2002).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-237/S-012." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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If you have any questions, call Kalyani Bhatt, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Katherine OConnell
4/18/03 03:48:55 PM
acting as Division Director today for Jonathan Wilkin, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

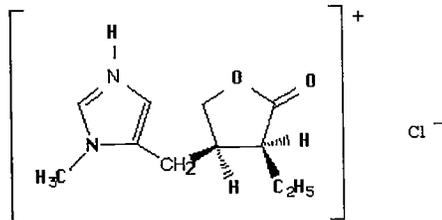
APPLICATION NUMBER:

NDA 20-237/S-012

APPROVED LABELING

SALAGEN[®] Tablets
(pilocarpine hydrochloride)

DESCRIPTION: SALAGEN[®] Tablets contain pilocarpine hydrochloride, a cholinergic agonist for oral use. Pilocarpine hydrochloride is a hygroscopic, odorless, bitter tasting white crystal or powder which is soluble in water and alcohol and virtually insoluble in most non-polar solvents. Pilocarpine hydrochloride, with a chemical name of (3*S*-*cis*)-2(3*H*)-Furanone, 3-ethylidihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl] monohydrochloride, has a molecular weight of 244.72.



Each 5 mg SALAGEN[®] Tablet for oral administration contains 5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet, the tablet's film coating, and polishing are: carnauba wax, hydroxypropyl methylcellulose, microcrystalline cellulose, stearic acid, titanium dioxide and other ingredients.

Each 7.5 mg SALAGEN[®] Tablet for oral administration contains 7.5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet, the tablet's film coating, and polishing are: carnauba wax, hydroxypropyl methylcellulose, microcrystalline cellulose, stearic acid, titanium dioxide, FD&C blue # 2 aluminum lake, and other ingredients.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: Pilocarpine is a cholinergic parasympathomimetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action. Pilocarpine, in appropriate dosage, can increase secretion by the exocrine glands. The sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands and the mucous cells of the respiratory tract may be stimulated. When applied topically to the eye as a single dose it causes miosis, spasm of accommodation, and may cause a transitory rise in intraocular pressure followed by a more persistent fall. Dose-related smooth muscle stimulation of the intestinal tract may cause increased tone, increased motility, spasm, and tenesmus. Bronchial smooth muscle tone may increase. The tone and motility of urinary tract, gallbladder, and biliary duct smooth muscle may be enhanced. Pilocarpine may have paradoxical effects on the cardiovascular system. The expected effect of a muscarinic agonist is vasodepression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

In a study of 12 healthy male volunteers there was a dose-related increase in unstimulated salivary flow following single 5 and 10 mg oral doses of SALAGEN[®] Tablets. This effect of pilocarpine on salivary flow was time-related with an onset at 20 minutes and a peak effect at 1 hour with a duration of 3 to 5 hours (See **Pharmacokinetics** section).

Head & Neck Cancer Patients: In a 12 week randomized, double-blind, placebo-controlled study in 207 patients (placebo, N=65; 5 mg, N=73; 10 mg, N=69), increases from baseline (means 0.072 and 0.112 mL/min, ranges -0.690 to 0.728 and -0.380 to 1.689) of whole saliva flow for the 5 mg (63%) and 10 mg (90%) tablet, respectively, were seen 1 hour after the first dose of SALAGEN[®] Tablets. Increases in unstimulated parotid flow were seen following the first dose

(means 0.025 and 0.046 mL/min, ranges 0 to 0.414 and -0.070 to 1.002 mL/min for the 5 and 10 mg dose, respectively). In this study, no correlation existed between the amount of increase in salivary flow and the degree of symptomatic relief.

Siogren's Syndrome Patients: In two 12 week randomized, double-blind, placebo-controlled studies in 629 patients (placebo, n=253; 2.5 mg, n=121; 5 mg, n=255; 5-7.5 mg, n=114), the ability of SALAGEN[®] Tablets to stimulate saliva production was assessed. In these trials using varying doses of SALAGEN[®] Tablets (2.5-7.5 mg), the rate of saliva production was plotted against time. An Area Under the Curve (AUC) representing the total amount of saliva produced during the observation interval was calculated. Relative to placebo, an increase in the amount of saliva being produced was observed following the first dose of SALAGEN[®] Tablets and was maintained throughout the duration (12 weeks) of the trials in an approximate dose response fashion (See **Clinical Studies** section).

Pharmacokinetics: In a multiple-dose pharmacokinetic study in male volunteers following 2 days of 5 or 10 mg of oral pilocarpine hydrochloride tablets given at 8 a.m., noontime, and 6 p.m., the mean elimination half-life was 0.76 hours for the 5 mg dose and 1.35 hours for the 10 mg dose. T_{max} values were 1.25 hours and 0.85 hours. C_{max} values were 15 ng/mL and 41 ng/mL. The AUC trapezoidal values were 33 h(ng/mL) and 108 h(ng/mL), respectively, for the 5 and 10 mg doses following the last 6 hour dose.

Pharmacokinetics in elderly male volunteers (n = 11) were comparable to those in younger men. In five healthy elderly female volunteers, the mean C_{max} and AUC were approximately twice that of elderly males and young normal male volunteers.

When taken with a high fat meal by 12 healthy male volunteers, there was a decrease in the rate of absorption of pilocarpine from SALAGEN[®] Tablets. Mean T_{max} 's were 1.47 and 0.87 hours, and mean C_{max} 's were 51.8 and 59.2 ng/mL for fed and fasted, respectively.

Limited information is available about the metabolism and elimination of pilocarpine in humans. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. Pilocarpine and its minimally active or inactive degradation products, including pilocarpic acid, are excreted in the urine. Pilocarpine does not bind to human or rat plasma proteins over a concentration range of 5 to 25,000 ng/mL. The effect of pilocarpine on plasma protein binding of other drugs has not been evaluated.

In patients with mild to moderate hepatic impairment (n=12), administration of a single 5 mg dose resulted in a 30% decrease in total plasma clearance and a doubling of exposure (as measured by AUC). Peak plasma levels were also increased by about 30% and half-life was increased to 2.1 hrs.

There were no significant differences in the pharmacokinetics of oral pilocarpine in volunteer subjects (n=8) with renal insufficiency (mean creatinine clearances 25.4 mL/min; range 9.8 – 40.8 mL/min) compared to the pharmacokinetics previously observed in normal volunteers.

Clinical Studies: Head & Neck Cancer Patients: A 12 week randomized, double-blind, placebo-controlled study in 207 patients (142 men, 65 women) was conducted in patients whose mean age was 58.5 years with a range of 19 to 77; the racial distribution was Caucasian 95%, Black 4%, and other 1%. In this population, a statistically significant improvement in mouth dryness occurred in the 5 and 10 mg SALAGEN[®] Tablet treated patients compared to placebo treated patients. The 5 and 10 mg treated patients could not be distinguished. (See Pharmacodynamics section for flow study details.)

Another 12 week, double-blind, randomized, placebo-controlled study was conducted in 162 patients whose mean age was 57.8 years with a range of 27 to 80; the racial distribution was Caucasian 88%, Black 10%, and other 2%. The effects of placebo were compared to 2.5 mg three times a day of SALAGEN[®] Tablets for 4 weeks followed by adjustment to 5 mg three times a day and 10 mg three times a day. Lowering of the dose was necessary because of adverse events in 3 of 67 patients treated with 5 mg of SALAGEN[®] Tablets and in 7 of 66 patients treated with 10 mg of SALAGEN[®] Tablets. After 4 weeks of treatment, 2.5 mg of SALAGEN[®] Tablets three times a day was comparable to placebo in relieving dryness. In patients treated with 5 mg and 10 mg of SALAGEN[®] Tablets, the greatest improvement in dryness was noted in patients with no measurable salivary flow at baseline.

In both studies, some patients noted improvement in the global assessment of their dry mouth, speaking without liquids, and a reduced need for supplemental oral comfort agents.

In the two placebo-controlled clinical trials, the most common adverse events related to drug, and increasing in rate as dose increases, were sweating, nausea, rhinitis, diarrhea, chills, flushing, urinary frequency, dizziness, and asthenia. The most common adverse experience causing withdrawal from treatment was sweating (5 mg t.i.d. ≤1%; 10 mg t.i.d.=12%).

Sjogren's Syndrome Patients: Two separate studies were conducted in patients with primary or secondary Sjogren's Syndrome. In both studies, the majority of patients best fit the European criteria for having primary Sjogren's Syndrome. ["Criteria for the Classification of Sjogren's Syndrome" (Vitali C, Bombardieri S, Moutsopoulos HM, et al: Preliminary criteria for the classification of Sjogren's syndrome. *Arthritis Rheum* 36:340-347, 1993.)]

A 12-week, randomized, double-blind, parallel-group, placebo-controlled study was conducted in 256 patients (14 men, 242 women) whose mean age was 57 years with a range of 24 to 85 years. The racial distribution was as follows: Caucasian 91%, Black 6%, and other 3%.

The effects of placebo were compared with those of SALAGEN[®] Tablets 5 mg four times a day (20 mg/day) for 6 weeks. At 6 weeks, the patients' dosage was increased from 5 mg SALAGEN[®] Tablets q.i.d. to 7.5 mg q.i.d. The data collected during the first 6 weeks of the trial were evaluated for safety and efficacy, and the data of the second 6 weeks of the trial were used to provide additional evidence of safety.

After 6 weeks of treatment, statistically significant global improvement of dry mouth was observed compared to placebo. "Global improvement" is defined as a score of 55 mm or more on a 100 mm visual analogue scale in response to the question, "Please rate your present condition of dry mouth (xerostomia) compared with your condition at the start of this study. Consider the changes to your dry mouth and other symptoms related to your dry mouth that have occurred since you have taken this medication." Patients' assessments of specific dry mouth symptoms such as severity of dry mouth, mouth discomfort, ability to speak without water, ability to sleep without drinking water, ability to swallow food without drinking, and a decreased use of saliva substitutes were found to be consistent with the significant global improvement described.

Another 12 week randomized, double-blind, parallel-group, placebo-controlled study was conducted in 373 patients (16 men, 357 women) whose mean age was 55 years with a range of 21 to 84. The racial distribution was Caucasian 80%, Oriental 14%, Black 2%, and 4% of other origin. The treatment groups were 2.5 mg pilocarpine tablets, 5 mg SALAGEN[®] Tablets, and placebo. All treatments were administered on a four times a day regimen.

After 12 weeks of treatment, statistically significant global improvement of dry mouth was observed at a dose of 5 mg compared with placebo. The 2.5 mg (10mg/day) group was not significantly different than placebo. However, a subgroup of patients with rheumatoid arthritis tended to improve in global assessments at both the 2.5 mg q.i.d. (9 patients) and 5 mg q.i.d. (16 patients) dose (10-20 mg/day). The clinical significance of this finding is unknown.

Patients' assessments of specific dry mouth symptoms such as severity of dry mouth, mouth discomfort, ability to sleep without drinking water, and decreased use of saliva substitutes were also found to be consistent with the significant global improvement described when measured after 6 weeks and 12 weeks of SALAGEN[®] Tablets use.

INDICATIONS AND USAGE: SALAGEN[®] Tablets are indicated for 1) the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck; and 2) the treatment of symptoms of dry mouth in patients with Sjogren's syndrome.

CONTRAINDICATIONS: SALAGEN[®] Tablets are contraindicated in patients with uncontrolled asthma, known hypersensitivity to pilocarpine, and when miosis is undesirable, e.g., in acute iritis and in narrow-angle (angle closure) glaucoma.

WARNINGS:

Cardiovascular Disease: Patients with significant cardiovascular disease may be unable to compensate for transient changes in hemodynamics or rhythm induced by pilocarpine. Pulmonary edema has been reported as a complication of pilocarpine toxicity from high ocular doses given for acute angle-closure glaucoma. Pilocarpine should be administered with caution in and under close medical supervision of patients with significant cardiovascular disease.

Ocular: Ocular formulations of pilocarpine have been reported to cause visual blurring which may result in decreased visual acuity, especially at night and in patients with central lens changes, and to cause impairment of depth perception. Caution should be advised while driving at night or performing hazardous activities in reduced lighting.

Pulmonary Disease: Pilocarpine has been reported to increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Pilocarpine hydrochloride should be administered with caution to and under close medical supervision in patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease requiring pharmacotherapy.

PRECAUTIONS:

General: Pilocarpine toxicity is characterized by an exaggeration of its parasympathomimetic effects. These may include: headache, visual disturbance, lacrimation, sweating, respiratory distress, gastrointestinal spasm, nausea, vomiting, diarrhea, atrioventricular block, tachycardia, bradycardia, hypotension, hypertension, shock, mental confusion, cardiac arrhythmia, and tremors.

The dose-related cardiovascular pharmacologic effects of pilocarpine include hypotension, hypertension, bradycardia, and tachycardia.

Pilocarpine should be administered with caution to patients with known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis, and biliary obstruction.

Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic (or "ureteral reflux"), particularly in patients with nephrolithiasis.

Cholinergic agonists may have dose-related central nervous system effects. This should be considered when treating patients with underlying cognitive or psychiatric disturbances.

Hepatic Insufficiency: Based on decreased plasma clearance observed in patients with moderate hepatic impairment, the starting dose in these patients should be 5 mg twice daily, followed by

adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency (Child-Pugh score of 5-6) do not require dosage reductions. To date, pharmacokinetic studies in subjects with severe hepatic impairment (Child-Pugh score of 10-15) have not been carried out. The use of pilocarpine in these patients is not recommended.

Child-Pugh scoring system for Hepatic impairment

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg. Per 100 ml.)	1-2	2-3	>3
Albumin (g. per 100 ml.)	3-5	2.8-3.5	<2.8
Prothrombin time (sec. Prolonged)	1-4	4-6	>6
For primary biliary cirrhosis:- Bilirubin (mg. per 100 ml.)	1-4	4-10	>10

*According to grading of Trey, Burns, and Saunders (1966)

Reference: Pugh, R.N.H., Murray-Lyon, I.M., Dawson, J.L. Pietroni, M.C., Williams, R. 1973, Transection of the Oesophagus for Bleeding Oesophageal Varices, *Brit. J. Surg.*, 60:646-9.

Information for Patients: Patients should be informed that pilocarpine may cause visual disturbances, especially at night, that could impair their ability to drive safely.

If a patient sweats excessively while taking pilocarpine hydrochloride and cannot drink enough liquid, the patient should consult a physician. Dehydration may develop.

Drug Interactions: Pilocarpine should be administered with caution to patients taking beta adrenergic antagonists because of the possibility of conduction disturbances. Drugs with parasympathomimetic effects administered concurrently with pilocarpine would be expected to result in additive pharmacologic effects. Pilocarpine might antagonize the anticholinergic effects of drugs used concomitantly. These effects should be considered when anticholinergic properties may be contributing to the therapeutic effect of concomitant medication (e.g., atropine, inhaled ipratropium).

While no formal drug interaction studies have been performed, the following concomitant drugs were used in at least 10% of patients in either or both Sjogren's efficacy studies: acetylsalicylic acid, artificial tears, calcium, conjugated estrogens, hydroxychloroquine sulfate, ibuprofen, levothyroxine sodium, medroxyprogesterone acetate, methotrexate, multivitamins, naproxen, omeprazole, paracetamol, and prednisone.

Carcinogenesis, mutagenesis, impairment of fertility: Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage studied (up to 30mg/kg/day, which yielded a systemic exposure approximately 50 times larger than the maximum systemic exposure observed clinically). In rats, a dosage of 18mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both males and females, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats. The tumorigenicity observed in rats was observed only at a large multiple of the maximum labeled clinical dose, and may not be relevant to clinical use.

No evidence that pilocarpine has the potential to cause genetic toxicity was obtained in a series of studies that included: 1) bacterial assays (Salmonella and E. coli) for reverse gene mutations; 2) an *in vitro* chromosome aberration assay in a Chinese hamster ovary cell line; 3) an *in vivo*

chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Oral administration of pilocarpine to male and female rats at a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on male animals, female animals, or both males and females. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day (approximately 3 times the maximum recommended human dose when compared on the basis of body surface area (mg/m^2) estimates) for six months resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair the fertility of male and female humans. SALAGEN[®] Tablets should be administered to individuals who are attempting to conceive a child only if the potential benefit justifies potential impairment of fertility.

Pregnancy: Teratogenic effects

Pregnancy Category C: Pilocarpine was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 mg/kg/day (approximately 26 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates). These effects may have been secondary to maternal toxicity. In another study, oral administration of pilocarpine to female rats during gestation and lactation at a dosage of 36 mg/kg/day (approximately 10 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates) resulted in an increased incidence of stillbirths; decreased neonatal survival and reduced mean body weight of pups were observed at dosages of 18 mg/kg/day (approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m^2) estimates) and above. There are no adequate and well-controlled studies in pregnant women. SALAGEN[®] Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SALAGEN[®] Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Head and Neck Cancer Patients: In the placebo-controlled clinical trials (see Clinical Studies section) the mean age of patients was approximately 58 years (range 19 to 80). Of these patients, 97/369 (61/217 receiving pilocarpine) were over the age of 65 years. In the healthy volunteer studies, 15/150 subjects were over the age of 65 years. In both study populations, the adverse events reported by those over 65 years and those 65 years and younger were comparable. Of the 15 elderly volunteers (5 women, 10 men), the 5 women had higher C_{max} 's and AUC's than the men. (See **Pharmacokinetics** section.)

Sjogren's Syndrome Patients: In the placebo-controlled clinical trials (see **Clinical Studies** section), the mean age of patients was approximately 55 years (range 21 to 85). The adverse events reported by those over 65 years and those 65 years and younger were comparable except for notable trends for urinary frequency, diarrhea, and dizziness (see **ADVERSE REACTIONS** section).

ADVERSE REACTIONS: Head & Neck Cancer Patients: In controlled studies, 217 patients received pilocarpine, of whom 68% were men and 32% were women. Race distribution was 91% Caucasian, 8% Black, and 1% of other origin. Mean age was approximately 58 years. The

majority of patients were between 50 and 64 years (51%), 33% were 65 years and older and 16% were younger than 50 years of age.

The most frequent adverse experiences associated with SALAGEN[®] Tablets were a consequence of the expected pharmacologic effects of pilocarpine.

Adverse Event	10 mg t.i.d. (30mg/day)	5 mg t.i.d. (15mg/day)	Placebo (t.i.d.)
	<u>n=121</u>	<u>n=141</u>	<u>n=152</u>
Sweating	68%	29%	9%
Nausea	15	6	4
Rhinitis	14	5	7
Diarrhea	7	4	5
Chills	15	3	<1
Flushing	13	8	3
Urinary Frequency	12	9	7
Dizziness	12	5	4
Asthenia	12	6	3

In addition, the following adverse events ($\geq 3\%$ incidence) were reported at dosages of 15-30 mg/day in the controlled clinical trials:

Adverse Event	Pilocarpine HCl 5-10 mg t.i.d. (15-30 mg/day)	Placebo (t.i.d.)
	<u>n=212</u>	<u>n=152</u>
Headache	11%	8%
Dyspepsia	7	5
Lacrimation	6	8
Edema	5	4
Abdominal Pain	4	4
Amblyopia	4	2
Vomiting	4	1
Pharyngitis	3	8
Hypertension	3	1

The following events were reported with treated head and neck cancer patients at incidences of 1% to 2% at dosages of 7.5 to 30 mg/day: abnormal vision, conjunctivitis, dysphagia, epistaxis, myalgias, pruritus, rash, sinusitis, tachycardia, taste perversion, tremor, voice alteration.

The following events were reported rarely in treated head and neck cancer patients (<1%):
Causal relation is unknown.

Body as a whole: body odor, hypothermia, mucous membrane abnormality
 Cardiovascular: bradycardia, ECG abnormality, palpitations, syncope
 Digestive: anorexia, increased appetite, esophagitis, gastrointestinal disorder, tongue disorder
 Hematologic: leukopenia, lymphadenopathy
 Nervous: anxiety, confusion, depression, abnormal dreams, hyperkinesia, hypesthesia, nervousness, paresthesias, speech disorder, twitching
 Respiratory: increased sputum, stridor, yawning
 Skin: seborrhea
 Special senses: deafness, eye pain, glaucoma
 Urogenital: dysuria, metrorrhagia, urinary impairment

In long-term treatment were two patients with underlying cardiovascular disease of whom one experienced a myocardial infarct and another an episode of syncope. The association with drug is uncertain.

Sjogren's Syndrome Patients: In controlled studies, 376 patients received pilocarpine, of whom 5% were men and 95% were women. Race distribution was 84% Caucasian, 9% Oriental, 3% Black, and 4% of other origin. Mean age was 55 years. The majority of patients were between 40 and 69 years (70%), 16% were 70 years and older and 14% were younger than 40 years of age. Of these patients, 161/629 (89/376 receiving pilocarpine) were over the age of 65 years. The adverse events reported by those over 65 years and those 65 years and younger were comparable except for notable trends for urinary frequency, diarrhea, and dizziness. The incidences of urinary frequency and diarrhea in the elderly were about double those in the non-elderly. The incidence of dizziness was about three times as high in the elderly as in the non-elderly. These adverse experiences were not considered to be serious. In the 2 placebo-controlled studies, the most common adverse events related to drug use were sweating, urinary frequency, chills, and vasodilatation (flushing). The most commonly reported reason for patient discontinuation of treatment was sweating. Expected pharmacologic effects of pilocarpine include the following adverse experiences associated with SALAGEN[®] Tablets:

Adverse Event	5 mg q.i.d. (20 mg/day) <u>n=255</u>	Placebo (q.i.d.) <u>n=253</u>
Sweating	40%	7%
Urinary Frequency	10	4
Nausea	9	9
Flushing	9	2
Rhinitis	7	8
Diarrhea	6	7
Chills	4	2
Increased Salivation	3	0
Asthenia	2	2

In addition, the following adverse events ($\geq 3\%$ incidence) were reported at dosages of 15-30 mg/day in the controlled clinical trials:

Adverse Event	Pilocarpine HCl 5 mg q.i.d. (20 mg/day) <u>n=255</u>	Placebo (q.i.d.) <u>n=253</u>
Headache	13%	19%
Flu Syndrome	9	9
Dyspepsia	7	7
Dizziness	6	7
Pain	4	2
Sinusitis	4	5
Abdominal Pain	3	4
Vomiting	3	1
Pharyngitis	2	5
Rash	2	3
Infection	2	6

The following events were reported with treated head and neck cancer patients at incidences of 1% to 2% at dosages of 7.5 to 30 mg/day: abnormal vision, conjunctivitis, dysphagia, epistaxis, myalgias, pruritus, rash, sinusitis, tachycardia, taste perversion, tremor, voice alteration.

The following events were reported rarely in treated Sjogren's patients (<1%) at dosing of 10-30 mg/day: Causal relation is unknown.

Body as a whole: chest pain, cyst, death, moniliasis, neck pain, neck rigidity, photosensitivity reaction
Cardiovascular: angina pectoris, arrhythmia, ECG abnormality, hypotension, hypertension, intracranial hemorrhage, migraine, myocardial infarction
Digestive: anorexia, bilirubinemia, cholelithiasis, colitis, dry mouth, eructation, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, hepatitis, abnormal liver function tests, melena, nausea & vomiting, pancreatitis, parotid gland enlargement, salivary gland enlargement, sputum increased, taste loss, tongue disorder, tooth disorder
Hematologic: hematuria, lymphadenopathy, abnormal platelets, thrombocythemia, thrombocytopenia, thrombosis, abnormal WBC
Metabolic and Nutritional: peripheral edema, hypoglycemia
Musculoskeletal: arthralgia, arthritis, bone disorder, spontaneous bone fracture, pathological fracture, myasthenia, tendon disorder, tenosynovitis
Nervous: aphasia, confusion, depression, abnormal dreams, emotional lability, hyperkinesia, hypesthesia, insomnia, leg cramps, nervousness, paresthesias, abnormal thinking, tremor
Respiratory: bronchitis, dyspnea, hiccup, laryngismus, laryngitis, pneumonia, viral infection, voice alteration
Skin: alopecia, contact dermatitis, dry skin, eczema, erythema nodosum, exfoliative dermatitis, herpes simplex, skin ulcer, vesiculobullous rash
Special senses: cataract, conjunctivitis, dry eyes, ear disorder, ear pain, eye disorder, eye hemorrhage, glaucoma, lacrimation disorder, retinal disorder, taste perversion, abnormal vision
Urogenital: breast pain, dysuria, mastitis, menorrhagia, metrorrhagia, ovarian disorder, pyuria, salpingitis, urethral pain, urinary urgency, vaginal hemorrhage, vaginal moniliasis

The following adverse experiences have been reported rarely with ocular pilocarpine: A-V block, agitation, ciliary congestion, confusion, delusion, depression, dermatitis, middle ear disturbance, eyelid twitching, malignant glaucoma, iris cysts, macular hole, shock, and visual hallucination.

MANAGEMENT OF OVERDOSE: Fatal overdosage with pilocarpine has been reported in the scientific literature at doses presumed to be greater than 100 mg in two hospitalized patients. 100 mg of pilocarpine is considered potentially fatal. Overdosage should be treated with atropine titration (0.5 mg to 1.0 mg given subcutaneously or intravenously) and supportive measures to maintain respiration and circulation. Epinephrine (0.3 mg to 1.0 mg, subcutaneously or intramuscularly) may also be of value in the presence of severe cardiovascular depression or bronchoconstriction. It is not known if pilocarpine is dialyzable.

DOSAGE AND ADMINISTRATION:

Regardless of the indication, the starting dose in patients with moderate hepatic impairment should be 5 mg twice daily, followed by adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency do not require dosage reductions. The use of pilocarpine in patients with severe hepatic insufficiency is not recommended. If needed, refer to the *Hepatic Insufficiency* subsection of the **Precautions** section of this label for definitions of mild, moderate and severe hepatic impairment.

Head & Neck Cancer Patients:

The recommended initial dose of SALAGEN[®] Tablets is 5 mg taken three times a day. Dosage should be titrated according to therapeutic response and tolerability. The usual dosage range is 15-30 mg per day. (Not to exceed 10 mg per dose.) Although early improvement may be realized, at least 12 weeks of uninterrupted therapy with SALAGEN[®] Tablets may be necessary to assess whether a beneficial response will be achieved. The incidence of the most common adverse events increases with dose. The lowest dose that is tolerated and effective should be used for maintenance.

Sjogren's Syndrome Patients:

The recommended dose of SALAGEN[®] Tablets is one tablet (5 mg) taken four times a day. Efficacy was established by 6 weeks of use.

HOW SUPPLIED:

SALAGEN[®] Tablets, 5 mg, are white, film coated, debossed round tablets, coded SAL 5. Each tablet contains 5 mg pilocarpine hydrochloride. They are supplied as follows:

NDC 58063-705-10 bottles of 100

Store at Controlled Room Temperature 15°-30°C (59°-86°F).

SALAGEN[®] Tablets, 7.5 mg, are blue, film coated, debossed round tablets, coded SAL 7.5. Each tablet contains 7.5 mg pilocarpine hydrochloride. They are supplied as follows:

NDC 58063-775-10 bottles of 100

Store at Controlled Room Temperature 15°-30°C (59°-86°F).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-237/S-012

CHEMISTRY REVIEW(S)

- A comprehensive description of the CMCs use to manufacture of the proposed 7.5 Salagen Tablet. The firm indicated that the same facility and equipment as described in the NDA was used. In addition, the methods of manufacture and the in-process control parameters are those in the approved NDA for the 5mg tablets (see Chemist's Review Notes for details).
- MGI requests FDA to waive the requirements for submission of evidence demonstrating the in vivo bioavailability or bioequivalence of the 7.5 Salagen Tablet based on concepts stipulated in various FDA guidelines and data supplied in the Bioavailability section.

Note: This information is deferred to Biopharm for comments. A review from Biopharm indicated that the MGI's request be granted.

18. **CONCLUSIONS AND RECOMMENDATIONS**

The CMCs were reviewed and found acceptable. Recommend approval letter to issue for this supplement. Final printed labeling should be requested.

Project manager should draft approval letter.

cc: Orig: NDA 20-237
HFD-540 HFD-540/MO
HFD-540/Pharm HFD-540/CSO
HFD-540/EGPappas HFD-540/WHDeCamp:R/D initialed

19. **REVIEWER**

NAME	SIGNATURE	DATE COMPLETED
Ernest G. Pappas		04/09/03

DISTRIBUTION ORIGINAL JACKET REVIEWER DIVISION FILE

7 Page(s) Withheld

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Ernest G. Pappas
4/9/03 11:00:38 AM
CHEMIST

Chemistry review is ready for signature. Recommend approval of
supplement; FPL should be requested.

Wilson H. DeCamp
4/9/03 11:17:29 AM
CHEMIST

concur with review; PM should prepare AP letter with
labeling for DivDir signature; action goal date is
4/20/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-237/S-012

**CLINICAL PHARMACOLOGY/
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review

Pilocarpine Hydrochloride Tablets 7.5mg

NDA 20-237, S-012

SALAGEN Tablets

Reviewer: E.D. Bashaw, Pharm.D.

MSWH

MGI Pharma, Inc.

Bloomington, MN

Submission Date:

Dec. 19, 2002

Review of a New Tablet Strength

Background

Salagen (pilocarpine hydrochloride) 5mg tablets were originally approved on March 22, 1994. They are indicated for the treatment of dry mouth secondary to radiation therapy in patients with head and neck cancer and for the treatment of dry mouth associated with Sjogren's Syndrome. The approved dose is 5 to 10mg three times a day. This supplement seeks approval of a 7.5mg tablet, which would represent an intermediate strength to the approved dosage forms and would allow for an increased flexibility in dosing. It should be noted that at the original time of approval the sponsor had plans on introducing a 7.5mg tablet as part of a labeling supplement for a new indication. In support of this indication would be in vivo clinical trials and a dissolution comparison of the 7.5mg tablet performance vs. the 5mg tablet in vitro using the F2 method. This supplement was not approved and plans for the new 7.5mg tablet were dropped.

In this supplement, the sponsor is pursuing the development of the 7.5mg tablet to provide dosing flexibility in the approved indications. As such the supplement consists of comparative formulation and in vitro dissolution data using the approved dissolution method for the 5 and 10mg tablets, no new clinical data is being provided.

Recommendation

On the basis of the information submitted in this supplement the request for a waiver of in vivo biostudies for the new Salagen 7.5mg tablet should be granted. We also recommend that the in vitro dissolution test specification be revised to $Q = 1 - \gamma$ at 30 min as the current specification ($Q = 1 - \gamma$ at 45min) is not in keeping with the actual dissolution performance of the product.

Dennis Bashaw, Pharm.D.

HFD-540/550/560

PK Review Team Leader

Secondary Review: Arzu Selen, Ph.D., Deputy Director, DPE-III _____

Formulation

Reproduced below is a comparative formulation table of the marketed 5mg tablet and the proposed 7.5mg tablet.

(↓error in table 7.5mg Tablet)

Ingredient (Function of excipients)	5 mg Tablet		7. mg Tablet		% Change of excipient out of total target tablet weight
	mg/tab	% of total tablet weight	mg/tab	% of total tablet weight	
Pilocarpine HCl USP (active)	5	/	7.5	/	/
Microcrystalline Cellulose, NF	/	/	/	/	/
Stearic Acid, NF	/	/	/	/	/
Blue	/	/	/	/	/
Carnauba Wax, NF	/	/	/	/	/
Total per Tablet	/	/	/	/	/

Examination of the table reveals that with the exception of the _____

In Vitro Release

At the time of the original NDA approval the sponsor submitted in vitro dissolution data in a number of media including, _____ Salagen tablets were highly soluble in all media dissolved in 30min). The approved dissolution test was the USP apparatus 2 at 50rpm with _____ The specification was set at _____ at 45 min. As part of the supplement the sponsor has conducted dissolution testing using three full size lots of

the 7.5mg tablet and a current production 5mg tablet for comparison. A graphical and tabular representation of the mean results is reproduced below

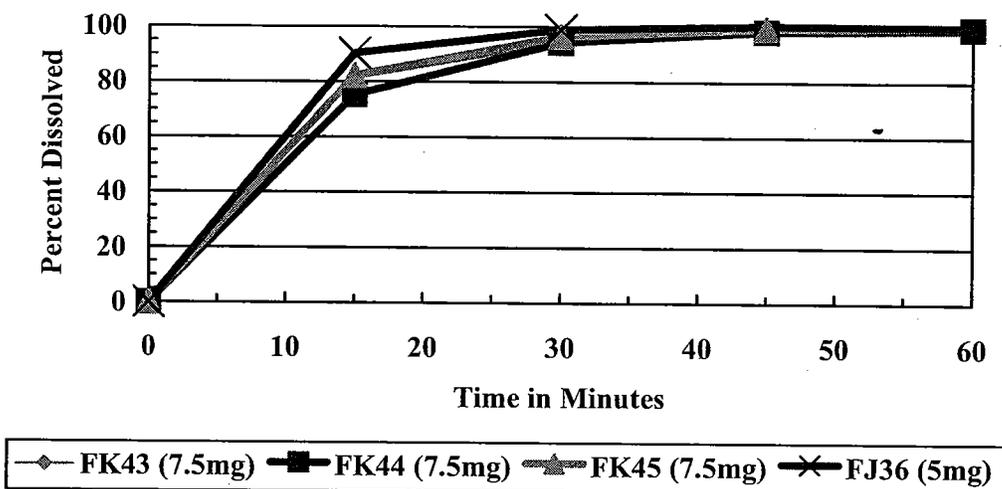


Table 6 Percent Dissolved by Lot for Salagen® Tablets

Time (min.)	Lot FK43 (7.5 mg)	Lot FK44 (7.5 mg)	Lot FK45 (7.5 mg)	Lot FJ36 (5 mg)
15	Mean: 82.2 Range: 71.0 - 92.7 % CV: 7.7	Mean: 75.2 Range: 66.3 - 89.6 % CV: 9.0	Mean: 82.3 Range: 70.9 - 100.7 % CV: 11.6	Mean: 90.3 Range: 82.9 - 96.8 % CV: 5.34
30	Mean: 95.1 Range: 89.7 - 98.5 % CV: 2.5	Mean: 94.3 Range: 91.6 - 96.8 % CV: 1.7	Mean: 96.5 Range: 90.8 - 103.1 % CV: 3.4	Mean: 99.0 Range: 92.9 - 102.1 % CV: 2.3
45	Mean: 97.4 Range: 93.9 - 99.3 % CV: 1.8	Mean: 98.4 Range: 96.1 - 100.8 % CV: 1.2	Mean: 99.5 Range: 96.9 - 103.2 % CV: 1.7	Mean: 100.2 Range: 97.4 - 102.4 % CV: 1.7
60	Mean: 98.1 Range: 93.9 - 100.2 % CV: 1.7	Mean: 99.4 Range: 96.7 - 101.6 % CV: 1.5	Mean: 100.1 Range: 97.7 - 103.5 % CV: 1.6	Mean: 100.5 Range: 96.2 - 102.2 % CV: 1.5

As one would expect from a HCl salt, Salagen tablets are very soluble. From this data one can see that dissolution is rapid and complete as evidenced by the decreasing %CV values as time goes on. This decrease in variability is due to the majority of the tablets demonstrating near 100% dissolution.

This being the case one has to wonder as to the adequacy of the current in vitro dissolution test as a measure of drug product quality. It is apparent from the above table that dissolution is essentially complete by 30min. (as evidenced by the observed very low %CV's). In setting dissolution specifications one must always balance performance with time. In this case it is apparent that a 45min timepoint and a specification of $\geq 95\%$ is very generous to a product that is more than $\geq 95\%$ dissolved at this timepoint. Clearly an improved specification would be $\geq 95\%$ at 30 min. One could consider even an earlier timepoint or more frequent sampling at prior to 30 min, but it has been the Agency's

experience that such specifications are highly variable due the rapid concentration changes taking place in the dissolution vessel.

F2 Analysis

As a demonstration of the similarity in dissolution between the 5 and 7.5mg tablets, the sponsor calculated the F2 Similarity Factor as contained in the SUPAC¹ document. From that guidance the F2 is stated as:

$$f_2 = 50 * \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} * 100 \right\}$$

where:

n = number of total time points (4)

R_t = dissolution value of the reference lot (FJ36) at time t

T_t = dissolution value of the test lot (FK43, FK44 or FK45) at time t

A similar dissolution profile is determined to exist if the F2 value is >50. Using the data from these four lots, we have the following results:

Lot	t (min.)	Mean % Dissolved	(T _t - R _t) ²	Σ(T _t - R _t) ²	* 1/n	+ 1	^-0.5	* 100	log	* 50	f ₂
FK43	15										
	30										
	45										
	60										
FK44	15										
	30										
	45										
	60										
FK45	15										
	30										
	45										
	60										
FJ36	15										
	30										
	45										
	60										

The results of F2 testing indicates that the 5 and 7.5mg tablets tested here have a similar dissolution profile. One criticism of this data is that the dissolution is so rapid that the drug is essentially at plateau even at the first timepoint of 15 min, making the discriminating power of the F2 somewhat reduced. While this is true, it should be noted

¹ Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation (Nov. 1995)

that even with one point the initial slow dissolution seen with lot FK44 is picked up with a lower F2 value than that seen with the other two 7.5mg lots. That being the case the overall solubility of pilocarpine HCl is such that by any standard it is a highly soluble drug. Whether or not it is a "highly permeable" drug ala the BCS classification system has yet to be demonstrated by the sponsor.

Discussion

In this supplement the sponsor has presented formulation and dissolution data in support of a new higher strength dosage form of Salagen (pilocarpine HCl) tablets. This tablet is intended to allow for a better dosing titration than is possible with the current 5mg tablet. While this is a higher strength tablet, thus this would be a "waiving up", it is a dose that is allowed for in the current approved dosing regimen of 5-10mg three times a day. This new dosage form would provide additional flexibility in dosing in that the current 5mg tablet is not scored for splitting and allows for only a 15 or 30mg total daily dose. Approval of the 7.5mg dose would allow for an intermediate dose of 22.5mg and could be useful in balancing side effects against efficacy. The 7.5mg tablets are similar in formulation to the 5mg tablet and demonstrate similar in vitro dissolution as evidenced by the F2 test. On the basis of this, and the fact that the resulting dosing regimen is contained in the current dosing recommendation, the requested waiver of in vivo biostudies should be granted.

In addition the in vitro dissolution test should be revised to reflect the actual observed dissolution performance as Q / / dissolved at 30min.

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/s/

Dennis Bashaw

2/15/05 09:52:24 AM

BIOPHARMACEUTICS

previously completed review, not put in DFS at time,
now putting it in system to mark assignment
completed

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-237/S-012

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



NDA 20-237/S-008; S-009; S-012

MGI Pharma, Inc.
Attention: Wendy L. Beck
Regulatory Affairs CMC Associate
5775 West Old Shakopee Road
Suite 100
Bloomington, MN 55437-3174

Dear Ms. Beck:

We acknowledge receipt of your June 9 and August 13, 2003 submissions, containing final printed labeling in response to our June 10, 2002, and April 18, 2003 letters approving your supplemental new drug applications for SALAGEN (pilocarpine hydrochloride) Tablets.

We have reviewed the labeling that you submitted in accordance with our June 10, 2002, and April 18, 2003 letters, and we find it acceptable.

If you have any questions, call Lea Carrington, Regulatory Project Manager, at 301-827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

12 Page(s) Withheld

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✓
_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Jonathan Wilkin
8/21/03 05:21:26 PM

Division of Dermatologic & Dental Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-237/S-008, 009 & 012

Name of Drug: Salagen (pilocarpine) Tablets

Applicant: MGI Pharma, Inc.

Material Reviewed:

Final Printed Labeling for NDA 20-237
SLR-008; SLR-009; SCS-012

Submission Date(s): November 14, 2002; June 9, 2003; August 13, 2003

Receipt Date(s): November 15, 2002; June 10, 2003; August 14, 2003

Background and Summary

SLR-008 dated September 29, 1997; approved June 10, 2002
SLR-009 dated February 22, 1999; approved June 10, 2002
SCS-012 dated December 19, 2002; approved April 18, 2003

Review

Comparison of the FPL submitted June 9, 2003 and August-13, 2003, to the labeling issued with the April 18, 2003 approval letter and subsequent changes agreed upon due to FDA errors in the issued labeling. The following was revealed:

Description: No changes noted.

Clinical Pharmacology: No significant changes noted.

Clinical Studies: No significant changes noted.

Indications and Usage: No changes noted.

Contraindications: No changes noted.

This is acceptable.

How Supplied: The statement, "Store at Controlled Room Temperature 15°–30°C (59°–86°F)" has been changed to

~~_____ / or the 5 mg tablets, _____~~
~~_____~~ for the 7.5 mg tablets.

This is acceptable, per Chemistry Team Leader, August 14, 2003.

~~_____~~
This is acceptable.

Conclusions

Final Printed Labeling is acceptable. An Acknowledge & Retain letter will be issued.

Suzanne Childs
Consumer Safety Technician

Supervisory Comment/Concurrence:

Mary Jean Kozma-Fornaro
Chief, Project Management Staff

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/s/

Suzanne Childs
8/20/03 07:41:12 AM
TECHNICAL

Mary Jean Kozma Fornaro
8/20/03 10:23:18 AM
CSO



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 18 April 2003

To: Winifred Wu	From: Melinda Harris Project Manager
Company: MCI Pharma	Division of Dermatologic & Dental Drug Products
Fax number: (952) 406-3289	Fax number: (301) 827-2091 or 2075
Phone number: (952) 406-3189	Phone number: (301) 827-2020
Subject: NDA 20-237 SCS 012	

Total no. of pages including cover:

Comments:

In the Head and Neck Cancer Patients subsection of the Dosage and Administration section of your proposed label, please replace the first three sentences with the following three sentences:

“Head & Neck Cancer Patients

The recommended initial dose of SALGEN® Tablets is 5 mg taken three times a day. Dosage should be titrated according to therapeutic response and / ~~—~~ / The usual dosage range is up to 15-30 mg per day (Not to exceed 10 mg per dose).”

Please send a fax back indicating if you agree with these changes.

Document to be mailed:

YES

NO

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/s/

Melinda Harris
4/18/03 02:26:08 PM
CSO

Dental Officer's Review of NDA 20-237
Supplement

<u>Drug:</u>	Salagen♦ Tablets (pilocarpine)	Serial Number:	SLR-012
		Submission date:	December 19, 2002
		Review date:	March 28, 2003
<u>Sponsor:</u>	MGI PHARMA	PDUFA date:	April 20, 2003
<u>Indication:</u>	Treatment of xerostomia induced by radiation therapy for head and neck cancers or secondary to Sjogren's syndrome.	<u>Pharmacologic Category:</u>	Cholinergic
		Project Manager:	Kalyani Bhatt
		Medical Reviewer:	Fred Hyman

Background:

Salagen® (pilocarpine), a cholinergic parasympathomimetic agent with predominant muscarinic action, was approved on March 22, 1994 for the treatment of symptoms of xerostomia due to salivary gland hypofunction resulting from radiotherapy to the head and neck. On February 11, 1998, an efficacy supplement to Salagen was approved which resulted in the addition of the indication, "treatment of symptoms of dry mouth in patients with Sjögren's syndrome." Salagen is currently only available in 5-mg tablets. The currently labeled dosing information for Head and Neck Cancer patients is as follows:

"The recommended initial dose of Salagen Tablets is one tablet (5 mg) taken three times a day. Dosage should be titrated according to therapeutic response and tolerance. The usual dosage range is up to 3-6 tablets or 15-30 mg per day. (Not to exceed 2 tablets per dose)."

In the current submission, the sponsor is proposing introduction of a 7.5-mg tablet to the marketplace to allow a greater range of dosing.

Resume:

There are three physical differences between the currently-marketed 5-mg tablet and the proposed 7.5-mg tablet: 1) Although the 5-mg and 7.5-mg tablets are the same weight and size, ~~the 5-mg tablet has FD&C blue #2 in addition to the titanium dioxide~~ the 7.5 mg tablet has FD&C blue #2 in addition to the titanium dioxide, and 3) The 5 mg tablet is debossed with "SAL 5" whereas the 7.5 mg tablet is debossed with "SAL 7.5". FDA reviewers from the Office of Biopharmaceutical Sciences, the Office of New Drug Chemistry, and the Division of Dermatologic and Dental Drug Products have all reviewed this submission. The biopharmaceutics reviewer has concluded that the 7.5-mg tablets may be approved because they are similar in formulation to the 5-mg tablet and demonstrate similar in vitro dissolution as evidenced by an F2 test. The assigned chemistry reviewer recommends an approval action as well pending agreeable labeling. The clinical reviewer finds the introduction of a 7.5-mg tablet acceptable, and has reviewed the revised labeling that resulted from this new strength. The change may be approved after the sponsor has made a suitable revision to the Dosage and Administration section of the label.

Proposed Changes in Labeling:

The sponsor proposed two changes to the package insert: one is in the *Description* section and the other is located in the and *How Supplied* section. The Agency also advises a change to the *Dosage and Administration* section. In this section of the review, each change will be stated and FDA comment will be given.

1. Description Section:

Current Labeling:

Each 5-mg SALAGEN♦ Tablet for oral administration contains 5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet, the tablet's film coating, and polishing are: carnauba wax, hydroxypropyl methylcellulose, microcrystalline cellulose, stearic acid, titanium dioxide and other ingredients.

Proposed Labeling:

Each 5-mg SALAGEN♦ Tablet for oral administration contains 5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet, the tablet's film coating, and polishing are: carnauba wax, hydroxypropyl methylcellulose, microcrystalline cellulose, stearic acid, titanium dioxide and other ingredients.

Each 7.5-mg SALAGEN♦ Tablet for oral administration contains 7.5 mg of pilocarpine hydrochloride. Inactive ingredients in the tablet, the tablet's film coating, and polishing are: carnauba wax, hydroxypropyl methylcellulose, microcrystalline cellulose, stearic acid, titanium dioxide, FD&C blue #2 aluminum lake, and other ingredients.

FDA Comment:

The addition of the second paragraph is acceptable. The additional ingredient in the 7.5 mg tablet is the FD&C blue #2 aluminum lake color, which was added to make the 7.5 mg tablet visually distinguishable from the white 5 mg tablet.

2. How Supplied:

Current Labeling

SALAGEN® Tablets, 5 mg are white, film coated, debossed round tablets, coded SAL 5. Each tablet contains 5 mg pilocarpine hydrochloride. They are supplied as follows:

NDA 58063-705-10 bottles of 100

Store at Controlled Room Temperature 15° – 30° C (59° – 86° F)

Proposed Labeling

SALAGEN® Tablets, 5 mg are white, film coated, debossed round tablets, coded

SAL 5. Each tablet contains 5 mg pilocarpine hydrochloride. They are supplied as follows:

NDC 58063-705-10 bottles of 100

Store at Controlled Room Temperature 15° – 30° C (59° – 86° F)

SALAGEN® Tablets, 7.5 mg are blue, film coated, debossed round tablets, coded SAL 7.5. Each tablet contains 7.5 mg pilocarpine hydrochloride. They are supplied as follows:

NDC 58063-775-10 bottles of 100

Store at Controlled Room Temperature 15° – 30° C (59° – 86° F)

FDA Comment:

The addition is acceptable.

3. Dosing and Administration (FDA initiated change)

Current labeling

There was no suggested change in the Dosage and Administration section of the proposed labeling to reflect the addition of the 7.5-mg tablet. It currently reads:

“Head & Neck Cancer Patients

The recommended initial dose of SALAGEN® Tablets is one tablet (5 mg) taken three times a day. Dosage should be titrated according to therapeutic response and tolerance. The usual dosage range is up to 3-6 tablets or 15-30 mg per day. (Not to exceed 2 tablets per dose).”

FDA Comment:

As currently stated, this section of the label is confusing and potentially dangerous, because the currently stated dose range of 3 – 6 tablets per day was written for 5-mg tablets and is too high if 7.5 mg tablets are used. Two tablets per dose as a maximum dose is also now incorrect without qualification.

Suggested Revision:

“Head & Neck Cancer Patients

The recommended initial dose of SALAGEN® Tablets is 5 mg taken three times a day. Dosage should be titrated according to therapeutic response and tolerance. The usual dosage range is up to 15-30 mg per day. (Not to exceed 10 mg per dose).”

Discussion:

Based upon the trials conducted and submitted for approval of both the head and neck cancer indication and the Sjogren's syndrome indication, there is already good support for the safety and efficacy of a 7.5 mg strength tablet. In addition, the current labeling of Salagen allows for a dosing of 5-10 mg tid for xerostomia from Head and Neck Radiation.

The reason for the current dosing and administration allowing for the range of 5 – 10 mg tid in the head and neck radiation are consistent with the results from those trials. As part of the protocol for the clinical trials in subjects with radiotherapy-damaged salivary glands, subjects started the trials with 2.5 mg tid dosing, and were allowed to increase to 5 mg tid, and then to 10 mg tid as they wished. The efficacy was established by a comparison of the combined 5 and 10 mg groups to placebo. The 2.5-mg dosing was no better than placebo, but the group dosed at 5-10 mg demonstrated an improvement. Although a 7.5-mg tablet already falls into the accepted dosing for the head and neck cancer indication, no 7.5-mg tablet was proposed at the time of approval for that indication.

For the Sjogren's syndrome indication, two pivotal trials were conducted. The first trial tested both 2.5 mg and 5.0 mg against placebo for 12 weeks. Efficacy was demonstrated for the 5-mg dose, but not for the 2.5-mg dose. Based on these results, the sponsor designed a second pivotal trial to test qid ingestion of a 5-mg tablet and a 7.5-mg tablet. All subjects started with 5-mg qid, but at 6 weeks, all subjects were switched to 7.5; to maintain blinding the placebo group was switched as well. Adverse events were recorded and incidences calculated for 114 subjects who were on the 7.5-mg dose and compared to the 5-mg dose and to placebo (See clinical review, NDA 20-237, SE1-007, February 4, 1998, pages 40-42). Although the Agency accepted the 7.5-gm dosing data in support of chronic safety (since the 7.5 mg dosing was greater than 5 mg), the Agency did not allow the Adverse Events section of the label to contain a separate 7.5 dose heading, since it would be confusing to the practitioner. The incidences of adverse events were similar between the 5-mg and 7.5 mg dosing, with expected outcomes such as increased sweating in the 7.5 group. The current label contains an adverse events section for the 5-10 mg tid dosing, which includes data from the 7.5-mg group, without specifically listing the 7.5-mg dosing regimen.

Since 7.5-mg tid dosing is within the currently labeled range for the head and neck cancer indication, it is likely that patients have been breaking 5-mg tablets in half for an intermediate dosing between the 5 and 10-mg dose. Since the 5-mg tablets are not scored, the introduction of the 7.5-mg tablet will provide a more accurate 7.5-mg dose.

Recommended Regulatory Action:

The sponsor's proposed changes to the Description section of the current label and the *How Supplied* section of the current label are acceptable. The sponsor should be informed that a change is necessary in the Dosage and Administration section to reflect the new 7.5 dose. The

suggested change from the Agency may be forwarded as a possibility. The sponsor should also be reminded that the Agency requested revisions on their current labeling during the next printing. (See FDA's supplement letter dated March 20, 2003, in response to the sponsor's FPL submission of November 14, 2002.) They should incorporate those changes into the revised label as well.

Frederick N. Hyman, D.D.S., M.P.H.

cc: HFD-540/Div File
HFD-540/DD/Wilkin
HFD-540/DTL/Kelsey
HFD-540/PM/Bhatt
HFD-830/Decamp/Pappas
HFD-880/Bashaw

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/s/

Fred Hyman
4/2/03 03:41:07 PM
MEDICAL OFFICER

John Kelsey
4/9/03 10:00:43 AM
MEDICAL OFFICER

Jonathan Wilkin
4/13/03 05:59:18 PM
MEDICAL OFFICER

Approval contingent on proposed labeling changes by dental officer.



Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 11, 2003

Number of Pages 2
(Including cover sheet) -

TO: Winifred C. Wu, RPH, MBA
COMPANY: MGI Pharma
FAX #: 952-406-3289

MESSAGE: Please see the following comments from the BioPharm Reviewer for
NDA 20-237, S-12 Salagen (pilocarpine hydrochloride) Tablets

FROM: Kalyani Bhatt
TITLE: Project Manager
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Please see the following comments for NDA 20-237 S-12:

On page 3, under item 3 the sponsor has the following statement:

The same dissolution test and specifications are used for the approved 5mg tablets and the proposed 7.5mg tablet. The specification is ~~100%~~ in 45 minutes....

However, in the MGI Pharma SOP, page 27, the sponsor states under item H the following:

"The limit Q is ~~100%~~ in 45 minutes as follows:"

The question thus is, What dissolution specification are they using as a release test?

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/s/

Kalyani Bhatt
3/11/03 10:02:32 AM
CSO