CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-237/S-007

MEDICAL REVIEW(S)

Dental Officer's Review of NDA 20-237

Efficacy Supplement

Drug:
Salagen® Tablets (pilocarpine hydrochloride)

Sponsor:
MGI PHARMA

Proposed indication:
Treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome

Pharmacologic Category:
Cholinergic

Project Manager: Roy Blay

Serial Number: SE1-007

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PDUFA date: February 11, 1998

Reviewer: Fred Hyman

Introduction:

Sjögren's syndrome (SS) is an immunologic disorder characterized by progressive destruction of the exocrine glands leading to mucosal and conjunctival dryness. SS has attracted growing interest and the disease definition has been broadened to encompass multiple immunological and serological abnormalities. The disease can occur by itself (primary SS), or in association with other autoimmune diseases (secondary SS). The disease has a bimodal age of onset. Primary Sjögren's is common in women in the fifth or sixth decades of life.

While virtually any organ system of the body may be affected in the patient with SS, the disease process is usually most striking in the salivary and lacrimal glands, where there is a progressive mononuclear cell infiltrate which generally leads to scarring. Residual glandular epithelial cells are often present at the periphery of the lobule. Loss of exocrine function accompanying these tissue changes are responsible for many of the clinical manifestations of SS, including the profound dryness of conjunctival and mucosal surfaces.

The major clinical symptoms are xerostomia and keratoconjunctivitis sicca. Patients complain of a gritty, dry, burning, or itching sensations in the eyes and severe dryness of the mouth. Lack of saliva may cause oral discomfort, pain, inflammation, mucositis, dysgeusia, angular cheilitis, increased caries and periodontal disease. A diagnosis of primary SS is usually made when the triad of keratoconjunctivitis sicca, xerostomia, and mononuclear infiltrate and/or serological abnormalities are noted. Xerostomia and/or keratoconjunctivitis may accompany a connective tissue disease, particularly rheumatoid arthritis. This is referred to as secondary

SS. The differential diagnosis of SS includes sarcoidosis, lymphoma, primary amyloidosis, HIV infection, and graft-verses-host disease.

Treatment is geared toward symptomatic relief of mucosal dryness and meticulous oral hygiene and includes artificial tears, ophthalmologic lubricating ointments, nasal sprays of normal saline, moisturizing skin lotions, frequent sipping of water, artificial saliva preparations and oral fluoride treatments.

Pilocarpine is the chief alkaloid obtained from the leaflets of South American shrubs of the genus *Pilocarpus*. This alkaloid, depending on dosing, can cause marked pharmacologic stimulation of exocrine glands in man producing among other actions, diaphoresis, salivation, lacrimation, gastric secretion, pancreatic secretion, hiccough, nausea, vomiting and weakness. Pilocarpine hydrochloride mechanistically exerts its beneficial effect through cholinergic stimulation of salivary secretions from residual major and minor functional salivary gland tissue. It is through this action, stimulation of exocrine secretions, that pilocarpine produces increased salivary and lacrimal responses which may in turn alleviate symptoms of dry mouth and dry eye.

Background and Regulatory History:

Salagen® (pilocarpine), a cholinergic parasympathomimetic agent with predominant muscarinic action, was approved on March 22, 1994 for treatment of symptoms of xerostomia due to salivary gland hypofunction resulting from radiotherapy to the head and neck. In the placebo-controlled studies conducted and evaluated for the approval of Salagen for providing significant symptomatic relief to patients suffering form post-radiation xerostomia, Salagen significantly improved symptoms of intraoral dryness, increased intraoral comfort, improved the ability to speak and improved the overall condition of xerostomia in the target patient population. Patients treated with Salagen tablets had diminished need for oral comfort agents such as artificial saliva, water, hard candy, etc. Salagen produced significantly increased salivary flow measured as either whole saliva or from parotid gland secretions.

After the review of a labeling supplement SLR-05 (submitted March 28, 1996), the sponsor was allowed to make two of three proposed labeling changes in the packet insert. The accepted changes included one that removed a warning about a reported association of ocular pilocarpine use and retinal detachment, and the other that changed its original warning against use in patients with cardiovascular disease to patients with *significant* cardiovascular disease. The rejected proposed revision was to remove a currently listed contraindication to taking the drug of narrow angle glaucoma. On May 31, 1996, another labeling supplement (SLR-006) was submitted for review in which the sponsor had suggested several revisions to its packet insert for Salagen® Tablets including the following sections: Clinical Pharmacology (pharmacokinetics); Warnings (pulmonary disease); Precautions (Carcinogenesis, mutagenesis, impairment of fertility, Pregnancy Category C, and Pediatrics); Adverse Reactions (chart); and

a change in Dosage and Administration. An action letter was sent on March 11, 1997 to which an approved label was attached. The revisions to the adverse reactions chart, pharmacokinetics, and dosage and administration section (advising that patients may need to take Salagen for up to 12 weeks to observe an improvement) were acceptable. The carcinogenesis, mutagenesis, impairment of fertility, and pregnancy category C changes were not accepted as proposed; the toxicologist proposed an alternative wording. Similarly, a warning for prospective patients with a history of pulmonary disease was not accepted, but a revision was suggested, as was also the case for a new Pediatrics precaution. The sponsor accepted all of the agency's revisions to their proposed label and this version is currently in use.

The current NDA efficacy supplement submission includes the results of two pivotal trials, conducted under the same IND as the original NDA submission. The objective of these trials, Protocols 92-01 and 92-02, was to assess the safety and efficacy of Salagen Tablets administered orally as a treatment for the symptoms of dry mouth and dry eyes associated with Sjögren's syndrome. These protocols were submitted to the agency in February, 1995 and reviewed by the surgical drug reviewer in HFD-160. Three amendments were submitted to the Agency for study P92-01. The first amendment (July 14, 1993) eliminated the need to meet scoring requirements for the Schirmer Tear test and Rose Bengal Stain test and limited the number of centers from which saliva samples would be collected for analyses. Although the Schirmer and Rose Bengal tests continued to be a part of the screening process, the candidates could enter the study if the scores did not meet the required range but all other study requirements were met. However, for those subjects whose scores did not meet the range, the objective ocular procedures would not be conducted during the study. The sponsor implemented this change due to the high ocular screen failure rate - failing scores were both below and above the scoring requirements. The questionnaire for the dry eyes continued without change for all study subjects. Both the objective and subjective measurements of dry eyes were changed from primary to secondary endpoints.

The second amendment (December 29, 1994) eliminated the objective assessment of ocular efficacy from Study P92-01. The Schirmer Tear test and Rose Bengal Stain procedures were still to be recorded during the screening procedures, but these measurements were not to be made during the study.

The third amendment (May 31, 1996) changed the primary measure of xerostomia from a singular question on dryness of the mouth to a global question. This amendment occurred prior to examining the database.

Executive Summary:

In this NDA efficacy supplement, the sponsor has submitted data and supporting documents in order to obtain a new indication for Salagen. The currently approved indication is treatment of

symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck; the sponsor's proposed expanded indication would also include treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome. After thorough review, the claim "treatment of symptoms of dry eyes in patients with Sjögren's syndrome" was disallowed because the sponsor has not successfully demonstrated improvement in dry eye symptoms with objective outcome measures. "Treatment of symptoms of dry mouth in patients with Sjögren's syndrome" has been shown by the sponsor to be a safe and valid new claim for Salagen at a dosing of 5 mg q.i.d.

Efficacy

Results of two Phase 3 trials as well as preliminary safety results of one in-progress, open-label study were submitted to this supplement. The two pivotal trials, P92-01 and P92-02, were both randomized, double-blinded, and placebo-controlled. The first of the two controlled SS trials, P92-01, was a parallel-group design in which 373 subjects were enrolled, with assignment made to one of 3 groups: placebo, 2.5 mg q.i.d. dose, and 5.0 mg q.i.d. dose. The trial was of 12 weeks duration, with outcome measurements made at baseline, week 6 and week 12. Efficacy was demonstrated for the 5 mg dose, but not for the 2.5 mg dose. Based on these results, the sponsor eliminated further testing of the 2.5 mg dose, and designed a second pivotal trial, P92-02, to test both 5 and 7.5 mg strength q.i.d. dosing. Trial 92-02 was a cross-over trial, with 256 subjects assigned to either a placebo or treatment group. Although it, too, was of 12 weeks duration, the trial was designed so that at Week 6, the subjects on placebo remained on the placebo, whereas the subjects on the 5.0 mg q.i.d. dosing were switched to 7.5 mg q.i.d. dosing. (To maintain blinding, the placebo group was also switched to another placebo). The blind was to have been maintained during the entire trial, although all subjects were told that if they developed bothersome adverse experiences after six weeks, they could return to the test medication that they had received during the first 6 weeks of the trial.

The primary outcome measurement in both trials was "global assessment of dry mouth" at endpoint, which was measured using a 100 mm visual analogue scale (VAS). This self-assessment requested that the subject, "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." Response to the visual analogue scale was categorized as worsening/non-responder (<45), no change/non-responder (45 - 55), or improvement/responder (>55). The percentage of responders in each treatment group was compared using non-parametric methods. Additional endpoints included a global ophthalmologic assessment, responses to additional VAS questions about dry mouth and dry eyes (such as decreased use of saliva substitutes, and reduced use of tear substitutes) and miscellaneous questions concerning dryness of skin, nasal passages, and the vagina. Sialometry was conducted in both trials; however, the sponsor did not choose sialometry results as a primary outcome variable, since MGI Pharma does not consider salivary function

improvement alone clinically significant without a concomitant improvement in patient assessment of clinical symptoms.

Although it is known that some of the subjects in the second pivotal trial did in fact switch back from 7.5 mg q.i.d. to their original 5 mg q.i.d. dosing, the sponsor did not present data that reported safety and efficacy separately by dose for this second trial. The sponsor reported the efficacy data only as the placebo group versus the drug group. Therefore, the second half of the trial in which subjects were on either 5.0 or 7.5 mg Salagen® is not interpretable in terms of efficacy, and is only usable for safety evaluation to a limited extent. In addition, because the 7.5 dose was tested only in the second trial, the FDA requirement of two or more trials to support this dosing are not met, even if the second one were able to demonstrate efficacy. Furthermore, because the tablets are supplied only as 5 mg. tablets, 7.5 mg dosing is not currently a possibility without having patients split tablets for each dose. However, in spite of the design flaw in the second protocol which disallowed the 7.5 mg data from being sufficient to support a 7.5 mg q.i.d. dosing, the Agency is satisfied that the 5.0 mg strength is efficacious for improving symptoms of dry mouth in patients with SS. The Agency reasoned that the 5.0 strength of Salagen, which was tested against placebo for the first 6 weeks of the second pivotal trial, was highly significant in demonstrating the dry mouth indication. This, coupled with a full 12 weeks of testing for the 5 mg strength in the first pivotal trial, fulfills the Agency's requirement for efficacy demonstration.

The additional variables pertinent to dry mouth symptoms were for the most part statistically significant in both trials at an α level of 0.05. Based upon review of minutes of past discussion with the sponsor, it has been decided that rather than consider the VAS data from the questionnaire as secondary endpoints, they will be considered as further descriptors of the global dry mouth question. True secondary endpoints in clinical trials, if successfully demonstrated, may be used to support truthful labeling. In the sponsor's proposed label, they have picked and chosen several of the VAS subquestions to include. Because these questions were not presented as separate endpoints, and because there exists a high degree of correlation between them and between the primary global question, it is difficult to assess the statistical significance of such comparisons. As a result, extracting certain of the questions to include in the label as the sponsor has proposed may be misleading without presenting them all and taking a statistical penalty for multiple comparisons. It is suggested that the label include examples of the more clinically related questionnaire responses as descriptors of the primary outcome, rather than portraying the response to these questions as separate endpoints on their own. In these SS trials, the salivary flow rate changes were highly significant in the treated group compared to placebo in both trials. Although this outcome is not necessarily well-correlated to the subject's perception of dryness, it is nonetheless consistent and supportive of Salagen's efficacy. The salivary flow, while supportive of the primary efficacy variable, is not best classified as a secondary endpoint. These flow results should be more appropriately thought of as pharmacodynamic parameters, and as such, will appear in the pharmacodynamics section of the label, a subsection of Clinical Pharmacology. Examination of flow rates was largely

performed to record the peak time of salivary flow to support the dosing of the drug, rather than demonstrate efficacy. The questions concerning dryness of skin, nasal passages, and the vagina were determined not to be supportive of the primary outcome variable, dry mouth. As such, these outcome variables would need to be considered as separate indications from either dry eyes or dry mouth, and will not be included in the final label for this efficacy supplement.

In spite of the shortcomings of the trials listed in this summary, both trials were capable of demonstrating a valid and highly significant primary outcome variable (improvement in global assessment of dry mouth) in subjects receiving the 5 mg q.i.d. dosing. Although the dry eyes indication was not adequately supported by the evidence provided, the data does successfully support approval of the drug for the dry mouth portion of the "dry eyes and dry mouth" claim. With several modifications to the proposed labeling, the final label will reflect what the studies have accurately demonstrated. All of these changes will be discussed in further detail in the main part of the review.

Safety

From the outset, it must be stated that the safety of Salagen at a greater dosing than the one being recommended for this indication has been thoroughly reviewed during the review of the original NDA for this drug. Because of differences that may exist between patients with dry mouth from Sjögren's syndrome and patients who have dry mouth as a result of head and neck cancer radiotherapy, the following data submitted in support of safety were examined and summarized in this review: adverse experiences reported by subjects on the trials, vital signs, electrocardiogram findings, and clinical laboratory evaluations.

Laboratory evaluations revealed that 4% of the pilocarpine group and 3% of the placebo group had shifts in laboratory test results. No subjects discontinued from either study because of a laboratory abnormality. A total of four subjects had abnormal electrocardiogram findings that were reported as adverse experiences, none of which were judged related to the test article.

Adverse experience data were presented from the two pivotal trials, as was limited data from the ongoing open-label trial. Most of the reported adverse experiences that demonstrated a statistically significant difference between test group and placebo were expected with a parasympathomimetic agent such as pilocarpine. This included sweating, urinary frequency, vasodilation, chills, and increased salivation. The statistically significant occurrence of edema and pruritus in the pilocarpine group was determined to be spurious, as there was no dose-response observed in the trend. Because of the multiple comparisons performed among the 50 adverse experiences with an incidence of > 1% reported, the p values obtained with comparisons must be analyzed with caution. For completeness, the label includes a tabled listing of all adverse events reported at an incidence of ≥ 3%, regardless of any causal relation to Salagen, and a listing of all events occurring at less than 3%. None of the serious adverse events reported were determined to be related to the pilocarpine.

Definition of Sjögren's syndrome

According to the sponsor, the majority of patients (580/629; 92.2%) entered into their SS studies meet the European criteria of SS; however, it appears as though this percentage was a result of a *post hoc* analysis, rather than as a result of inclusionary criteria. It clearly would have been a superior trial design for the sponsor to have stated this in their inclusionary criteria to ensure uniformity in recruitment, rather than to fit the subjects' profiles after the fact. Nonetheless, the European definition of SS is well-recognized and nearly all of the subjects enrolled in the trials met these criteria. To identify the patient population appropriately for the new indication, the label should include the definition of SS by which subjects in the clinical trials were judged.

The sponsor submitted an application for Orphan Drug status on August 29, 1991. In this application, the sponsor estimated the total number of individuals in the U.S. who suffer from SS as less than 200,000. According to the sponsor's orphan application, this was derived from criteria set forth by Dr. Robert Fox, whose criteria are very specific - much more so than the screening and SS definition employed in the sponsor's protocols. The sponsor did not use objective criteria as set forth by Dr. Fox in his criteria for recruitment, so the extrapolated number of eligible individuals in the US who meet the sponsor's criteria as defined in these clinical trials is probably significantly greater than their original estimate. The sponsor further contends in their orphan application that only 50% of SS patients are the target population for treatment with Salagen, because 25% of SS patients have little or no remaining glandular function and would not benefit from pilocarpine, and the other 25% do not have sufficiently severe xerostomia to warrant systemic pilocarpine therapy. However, the sponsor did not specifically screen for these subjects in the trials, so that all levels of SS were eligible for enrollment. Therefore, a 50% reduction in patients eligible for benefit for Salagen is no longer correct, based upon this NDA supplement. This information will be conveyed to the Office of Orphan Products Development (HF-35).

Summary Table for Controlled Phase 3 Clinical Trials NDA 20-237 Efficacy Supplement

Trial		P92-01		P92-02	
Status		Completed 5/93		Completed 3/95	
Total Subjects Enrolled in each treatment group	2.5 mg dose	121		0	
	5 mg dose	127		0	
	5 or 7.5 mg dose	0		128	
	placebo	125		128	
Duration of trial		12 Weeks		6 weeks on 5 mg dose, 6 weeks on 7.5 mg dose	
Locations and Numbers in each center		Detroit, MI	37	Tacoma, WA	18
		Philadelphia, PA	28	North Miami Beach, FL	5
		Louisville, KY	25	Tucson, AZ	26
		Winston-Salem, NC	37	Chicago, IL	26
		LaJolla, CA	16	Birmingham, AL	17
		San Antonio, TX	13	Boston, MA	60
		Houston, TX	12	Denver, CO	21
		Scottsdale, AZ	8	Richmond, VA	20
		Minneapolis, MN	17	Farmington, CT	18
		San Diego, CA	62	Ft. Lauderdale, FL	0
		Seattle, WA	19	Pittsburgh, PA	24
		Chicago, IL	18	Boca Raton, FL	21
		Stony Brook, NY	22		
		Rochester, NY	15		
		Boston, MA	7		
		Wichita, KS	12		
		Dallas, TX	25		
Global Assessment of Dry Mouth		Percent of subjects who reported ≥ 55 mm improvement on VAS scale and p-value associated with comparison to placebo.		Percent of subjects who reported ≥ 55 mm improvement on VAS scale and p-value associated with comparison to placebo.	
		Placebo	pilocarpine 5 mg	Placebo	pilocarpine 5 mg
	Week 6	31.4%	58.8% (p≤0.0001)	22.6%	46.3% (p≤0.0001)
	Week 12	32.4%	61.5% (p≤0.0001)	The 5 mg dosing was terminated at Week 6.	
Pivotal for	Efficacy?	Yes		Yes (through Week 6 only)	
	Safety?	Yes		Yes	
Comments				At Week 6, the subjects who were assigned to the 5 mg dosing group were switched to 7.5 mg dosing. Although results of the higher dosing are examined for safety, they cannot be used to support efficacy.	

Chemistry and Manufacturing Controls Summary:

The efficacy supplement required that two CMC issues be reviewed: 1) Additional 18-24 month stability data, and 2) an abbreviated Environmental Assessment. The chemist's recommendations were that a categorical exclusion claim for environmental assessment be granted due to the fact that the concentration of the active moiety is below the required 1.0 ppb. Based upon the stability data submitted, Salagen tablets are recommended for an expiry date of 30 months. The reviewer commented that as additional stability data becomes available, this expiration date can be extended. Refer to the chemistry review for full details.

Pharmacology/Toxicology Summary:

This submission contained reports of some new nonclinical studies that were performed with pilocarpine and resultant proposed changes in the labeling of Salagen to reflect the new data. The pharmacology reviewer concluded that administration of pilocarpine during pregnancy and lactation resulted in maternal toxicity at dosages of 18 and 36 mg/kg/day. No effects were observed on reproduction, behavior, or development of the tested animals. The reviewer recommended modifications to the sponsor's proposed labeling in the "Carcinogenesis, mutagenesis, impairment of fertility" and "Pregnancy" sections. Refer to the pharmacology/toxicology review for details.

Pharmacokinetic Summary:

The reviewer from the Division of Biopharmaceutics has stated that there is no new pharmacokinetic information to review in this submission, and that he does have any concerns with the new indication for this drug.

Clinical Trials:

Pivotal Study P92-01
Protocol Design

Reviewer's comment: The following section is a reiteration of the sponsor's protocol as submitted in the original IND (and included in this NDA submission for completeness). Note that the future tense is used in this section because the protocol was proposed prior to conduct of the trial.

Phase: 3

Title: A Multi center, Randomized, Double-Blind, Placebo-Controlled Evaluation of Pilocarpine HCl for the Treatment of Xerostomia

Associated with Sjögren's Syndrome; Fixed Dose

Objective

a. To assess the efficacy of Salagen Tablets administered orally as a treatment for the symptoms of xerostomia associated with Sjögren's syndrome; and,

b. to evaluate the safety of orally administered Salagen Tablets in patients with Sjögren's syndrome.

Principal Investigators and Associated Study Site:

Site Number	Principal Investigator	Site Name/Address	Total Number of Subjects Enrolled
01	Francis G. LeVeque, D.D.S.	Harper Hospital Detroit, MI	37
02	Frederick B. Vivino, M.D.	Philadelphia Sjögren's Syndrome & Dry Mouth Treatment Center Presbyterian Medical Center of Philadelphia Philadelphia, PA	28
03	Zafrulla Khan, D.D.S.	J. Graham Brown Cancer Center Louisville, KY	25
04	Paul Lee Salisbury III, D.D.S.	Department of Dentistry Bowman Gray School of Medicine Winston-Salem, NC	37
05	Robert I. Fox, M.D., Ph.D.	Scripps Clinic & Research Foundation Division of Rheumatology/Department of Immunology LaJolla, CA	16
06	Norman Talal, M.D.	Department of Medicine University of Texas Health Science Center San Antonio, TX	13
07	Richard W. Yee, M.D.	University of Texas Health Science Center Department of Ophthalmology Houston, TX	12
08	Leroy W. Griffing, M.D.	Mayo Clinic Scottsdale Scottsdale, AZ	8
09	Nelson Rhondus, D.M.D.	Division of Oral Diagnosis and Radiology School of Dentistry Minneapolis, MN	17
10	Tram Tran-Johnson, Pharm.D.	California Neuropsychological Clinical Research Institute San Diego, CA	62
11	Daniel Furst, M.D.	Virginia Mason Research Center Seattle, WA	19

12	Michael Ellman, M.D.	University of Chicago School of Medicine Chicago, IL	18
13	Leo Sreebny, D.D.S.	Department of Biology & Pathology SUNY at Stony Brook Stony Brook, NY	22
14	Cyril Meyerowitz, D.D.S.	University of Rochester School of Dentistry Rochester, NY	15
15	Stephen Sonis, D.M.D., D.M.Sc.	Brigham and Women's Hospital Boston, MA	7
16	Frederick Wolfe, M.D.	Arthritis Research & Clinical Centers Wichita, KS	12
17	Ibtisam Al-Hashimi, B.D.S., Ph.D.	Baylor College of Dentistry Dallas, TX	25
Total Number of Subjects			373

APPEARS THIS WAY
ON ORIGINAL