Subjects With Abnormal Laboratory Values - Controlled Studies P92-01 and P-92-02

	Subject	Abnormal Laboratory Values	Intensity
P92-01			
	Pilocarpine HCL 5 mg		
		Low glucose level 41	Mild
		Serum CO_2 low	Mild
		Hematuria	Mild
		WBC/HPF 30-40	Mild
		ALT (SGPT) 54	Mild
		Thrombocytopenia	Mild
		Blood chemistry test AST (SGOT) high, value = 152 IU/L Blood chemistry test ALT (SGPT) high, value = 140 IU/L Urinalysis: ketones = +1	Moderate Moderate Mild
	Pilocarpine HCL 2.5 mg		
		Total protein labs out of range	Mild
		WBC labs out of range	Mild
		Polys labs out of range	Mild
		High sed rate	Mild
		Large increase in platelet count	Mild
		High RBC/HPF in urinalysis	Mild
		Elevated white count in urine	Mild
	Placebo		
		Liver function tests abnormal	Mild
		Uric acid lab value high	Mild
		Low polys in hematology	Mild
		Clinically significant change in cholesterol value = 281 mg/DI	Mild
		Low platelet count	Mild
		WBC/HPF 15-20	Moderate
P92-02			
	Pilocarpine 5-7.5 mg		
		Elevated total bilirubin	Mild
		Decreased platelets	Moderate
		1) SGOT elevated to 63 IU/L 2) SGPT elevated to 68 IU/L	1)Mild 2) Mild
		1) Elevated transaminases 2) Elevated WBC/hpf, urinalysis	1) Moderate 2) Mild
		RBC/hpf elevated	Mild
	Placebo		
		Increased WBC/hpf	Mild

Drug-Drug Interactions

There were no reports of drug toxicities during either pivotal trial. In trial 92-01, subjects were not enrolled who used beta blockers, pilocarpine for ophthalmic indications, and medications such as anticholinergics, tricyclic antidepressants, and antihistamines which produce dry mouth symptomatology. However, during the second trial (92-02), only the beta blockers and ophthalmic pilocarpine were exclusionary criteria, since the sponsor had great difficulty in recruiting subjects for the first trial. By including subjects taking these medications, that are commonly prescribed in patients with SS, the sponsor has provided supporting evidence that the drug is safe and effective in subjects taking these drugs as well as those who are not. The following tables list the concomitant medications that were used by at least 10% of the subjects in each arm and the numbers of subjects in each trial who used these medications.

Most Frequently Used Concomitant Medications(≥10% of Subjects in any Treatment Group) P92-01

Medications	Pilocarpine HCl				Placebo	
	2.5 mg (n=121)		5 mg (n=127)		n=125	
Acetylsalicylic Acid	21	17.4%	19	15.0%	22	17.6%
Artificial Tears	17	14.1%	26	20.5%	14	11.2%
Calcium	11	9.1%	14	11.0%	9	7.2%
Estrogens Conjugated	30	24.8%	34	26.8%	33	26.4%
Hydroxychloroquine Phosphate	33	27.3%	29	22.8%	42	33.6%
Ibuprofen	34	28.1%	37	29.1%	28	22.4%
Levothyroxine Sodium	22	18.2%	23	18.1%	27	21.6%
Medroxyprogesterone Acetate	13	10.7%	11	8.7%	22	17.6%
Methotrexate	12	9.9%	15	11.8%	13	10.4%
Multivitamins	13	10.7%	21	16.5%	14	11.2%
Naproxen	12	9.9%	17	13.4%	16	12.8%
Omeprazole	13	10.7%	14	11.0%	12	9.6%
Paracetamol	53	43.8%	49	38.6%	36	28.8%
Prednisone	46	38.0%	29	22.8%	23	18.4%

Most Frequently Used Concomitant Medications(≥10% of Subjects in any Treatment Group) P92-02

Medications	Pilocarpine HCl (n=128)		Placebo (n=128)	
Acetylsalicylic Acid	22	17.2%	19	14.8%
Artificial Tears	21	16.4%	19	14.8%
Calcium	13	10.2%	20	15.6%
Estrogens Conjugated	31	24.2%	41	32.0%
Hydroxychloroquine Phosphate	43	33.6%	27	21.1%
Ibuprofen	18	14.1%	20	15.6%
Levothyroxine Sodium	22	17.2%	22	17.2%
Medroxyprogesterone Acetate	9	7.0%	18	14.1%
Methotrexate	15	11.7%	-	-
Multivitamins	15	11.7%	20	15.6%
Naproxen	11	8.6%	14	10.9%
Paracetamol	23	18.0%	30	23.4%
Prednisone	53	41.4%	81	63.3%

Discussion

There were several flaws in the protocol design that were serious enough to require rejection of some of the sponsor's conclusions. One such flaw was the elimination of objective measurement of the ocular component of the indication, which resulted in the Ophthalmology reviewer's decision to reject the sponsor's claim that Salagen is effective in relieving the symptoms of dry eyes. Another flaw was the use of a large number of secondary endpoints, i.e., multiple questions that probed the subject's subjective determination of improvement, were quantified on a VAS scale, and analyzed statistically. In addition, the multiple dosing regimen employed in the pivotal trials makes determination of the optimal dosing difficult. The impact of each of these deficiencies will be discussed in greater detail in the remainder of this section.

In spite of these shortcomings, 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. For example, although the large number of questions in the VAS

questionnaire make meaningful interpretation difficult as secondary endpoints, they can be successfully addressed as further descriptors of the global dry mouth question and labeled as such. The salivary flow, which the sponsor also classified as a secondary endpoint, may be more appropriately thought of as a pharmacodynamic parameter, and will appear in the pharmacodynamics section of the label. The sponsor tested 2.5 mg, 5.0 mg and 7.5 mg dosing strengths in the pivotal trials, whereas their proposed label recommended 10 mg q.i.d. dosing. Although their data could not support this proposed dosing, the data from the trials sufficiently supported the use of a 5.0 mg dose q.i.d. as safe and effective. Finally, because there are many criteria for classification of SS in the literature, there was some concern about the sponsor's correct inclusionary criteria for subjects. A *post hoc* analysis of the subjects supported the acceptance of the European (Vitali et al) criteria for SS, and this will be stated on the label. All of these changes will be discussed in further detail in the remainder of this section of the review.

Ophthalmologic Endpoints

Although objective ocular measures were originally included in the sponsor's protocol for these pivotal trials, protocol amendments eliminated these measurements. Concomitantly, the global assessment of the dry eyes was changed from a primary outcome variable to a secondary variable. An Ophthalmology consult was provided by the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drugs (HFD-550) in order to review the results of the pivotal trials, and provide discussion and recommendation regarding the ocular component of this claim. The opinion of the Ophthalmology reviewer is that there were no objective criteria upon which to evaluate the treatment, and the differences observed in the symptoms are not considered clinically significant. The reviewer concluded that this efficacy supplement fails to provide support for the treatment of symptoms of dry eyes in patients with Sjögren's syndrome. Refer to the separate Ophthalmology review for full details and discussion.

The sponsor had expressed concern about the effect on approving the dry mouth claim if the dry eyes claim were rejected. The decision to allow approval of the dry mouth indication without concomitant approval of the dry eye indication was made because the dry mouth global assessment was a primary outcome variable in the final protocol, whereas the global assessment of dry eyes was listed as an additional endpoint.

Dosage and Administration Regimen

Currently, Salagen tablets are approved for use in doses up to 10 mg t.i.d. for treatment of dry mouth in head and neck cancer patients. This current labeling is based upon clinical trials in which the head and neck cancer subjects were given both 5 and 10 mg t.i.d. dosing. In the two pivotal trials used to support the current NDA efficacy supplement, the sponsor tested doses of 2.5 mg q.i.d., 5 mg q.i.d., and 7.5 mg q.i.d. The sponsor selected this dosing in the SS studies for the following reasons:

1. The sponsor suspected that adding a fourth dose each day would prolong efficacy due to the short plasma half-life of oral pilocarpine.
2. Dosing of 2.5 mg and 7.5 mg strength q.i.d. was included in the event that Sjögren's syndrome subjects were more responsive than were the head and neck cancer subjects.

On average, most patients with SS have higher rates of salivary flow than patients who have xerostomia from head and neck radiotherapy. As was demonstrated in the sponsor's original NDA submission, the majority of patients with xerostomia that results from head and neck radiotherapy have negligible unstimulated salivary production. In the clinical trials submitted for approval of the original indication, even the higher 10 mg. dosing still produced only a small increase in the salivary flow compared to placebo, although the patients consistently reported that their symptoms of dry mouth felt less severe. Because the severity of xerostomia in Sjögren's syndrome subjects enrolled in the clinical trials currently being examined was less than for the patients with radiation induced xerostomia, the expectation that a lower dose may be efficacious was reasonable, and test worthy. The first of the two controlled SS trials, 92-01, tested both the 2.5 mg and the 5 mg strength 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 eliminated further testing of the 2.5 mg dose, and designed the second pivotal trial to compare 5 and 7.5 mg strength q.i.d. dosing.

However, rather than have parallel groups assigned to the different dosages, the sponsor created two groups - a placebo group, and a drug group. The drug group used 5 mg for the first 6 weeks of the trial, and then was switched to 7.5 mg. for the second 6 weeks (to maintain blinding, the placebo group was also switched to another placebo). The subjects were instructed that they could return to the dosing that they received during the first 6 weeks if they experienced intolerable adverse experiences. Although it is known that subjects did in fact switch back to their original dose, the sponsor did not present data that reported safety and efficacy separately by dose. The sponsor reported the efficacy data only as the placebo group versus the drug group. Therefore, the second half of the trial 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.

In spite of the design flaw in the second protocol which disallowed the 7.5 mg data from being sufficient to support this 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. Although the rationale for testing this group

of subjects with a 2.5 mg or 7.5 mg. dosing is valid, dose response should ideally have been established before conduct of the pivotal trials. In this way, the pivotal trials could have been designed in a way that focused on efficacy, rather than being confounded with dosing ranges that made interpretation inconclusive. One of the recommendations that resulted from this review is that the sponsor consider additional testing to support higher doses for this new indication (See *Recommended Regulatory Action* section of this review.)

The Agency's decision concerning the acceptable evidence of the appropriate dose requires amendment of the sponsor's proposed dosing recommendations in their proposed label. In the label submitted with this application, the sponsor extrapolated from insufficient data gathered at the 7.5 mg q.i.d. dosing level on SS patients to conclude that 1) the dosing for head and neck cancer patients (the previously approved indication) could be increased from the previously approved 10 mg. t.i.d. to 10 mg. q.i.d.; and 2) 10 mg. dosing applies to patients with Sjögren's syndrome. The sponsor's currently proposed labeling in this NDA submission combines both the head and neck cancer patients and the SS patients by recommending that 5 or 10 mg of Salagen be taken 3 or 4 times per day. To accurately reflect what the trials demonstrated, the dosing should be separated for SS and head and neck cancer indications. A new section should be created for patients with SS that recommends 5 mg Salagen q.i.d., and the dosing information for patients with xerostomia from head and neck cancer should be maintained as is; that is, one or two 5 mg tablets t.i.d. Without a clinical trial testing 5 or 10 mg. q.i.d. dosing for head and neck cancer patients, this proposed dosing is unsupported. Likewise, without testing 10 mg dosing q.i.d. in SS patients, that dose is unsupported for labeling at this time.

Choice of Primary and Secondary Variables

Although only one primary efficacy variable was evaluated, a large number of additional efficacy variables was evaluated. The sponsor included six subjective measurements of dry mouth, an analysis of the salivary measure through sialometry, 14 additional comparisons of subjective questions of eye dryness, and three additional questions about the dryness of the skin, vagina and nasal passages.

During the initial protocol submission, and prior to beginning the trial, two primary endpoints were chosen - global assessment of dry mouth, and global assessment of dry eyes. However, the sponsor amended the protocol (See Regulatory History section of this review) so that there would be only one primary endpoint in these trials, global assessment of dry mouth, whereas global measurement of dry eyes became a secondary endpoint. Due to difficulties in recruiting sufficient numbers of subjects who met the objective criteria of dry eyes as measured by Rose Bengal and Schirmer's testing, the sponsor eliminated these objective measures from both the screening criteria and outcome measures. In order to claim improvement in symptoms of dry eyes, objective measures are required as a matter of policy. Ocular assessments as measured by subjective VAS scales alone have been judged by the reviewing ophthalmologist to be

insufficient.

Because the global assessment of dry eyes had been made a secondary outcome variable, failure to accept dry eye indications did not automatically preclude the drug from being approved for its primary indication of dry mouth alone. Global assessment of dry mouth is the only primary efficacy variable. Dry mouth assessment included both objective (salivary flow) and subjective measures of mouth dryness (VAS questionnaire). Although the sponsor did not clearly label the other variables as "secondary", the following "additional efficacy variables" were considered: all of the VAS questions on dryness of the mouth and eyes; additional measurements such as skin, nasal passages, and vaginal dryness; salivary flow measurement; and the global eye question.

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. The salivary flow, while supportive of the primary efficacy variable, overall dryness, 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. Examination of flow rates was largely implemented 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 to not 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.

True secondary endpoints in clinical trials, if successfully demonstrated, may be used to support truthful labeling. In the sponsor's proposed label, they have selectively included several of the VAS subquestions. 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 comparison. 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.

Salivary Flow

From the results of the trials of Salagen in subjects with xerostomia from head and neck radiation therapy, it was learned that although the salivary flow increased, there was a poor correlation between the VAS scores and the salivary flow. A decision was made during that review that the patient's perception of comfort is more clinically relevant than actual salivary

flow rates. During the development of the trials to test Salagen for the SS indication, sialometry was chosen as an objective measure of pharmacologic action related to the treatment of xerostomia. 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.

In these SS trials, the salivary flow rate changes were highly significant in the treated group compared to placebo in both trials. The mean AUC data in the study reports (See AUC table in Results section of this review) are referred to by the sponsor as "derived values." They do not refer to absolute pre-dose flow rates. They represent a calculated area under the curve for salivary flow during the post-dose collection period. 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. Refer to the pharmacokinetics review for further discussion of the salivary flow data.

Diagnosis and Severity of Sjögren's Syndrome in Subjects Enrolled

Dr. Robert Fox, the author of the chapter on Sjögren's syndrome in The Textbook of Rheumatology (*Fourth Edition*: Kelley, W.N. et al, W.B. Saunders Company, Pennsylvania, 1993.) states that both symptoms and objective signs of ocular dryness and dry mouth must be present to confirm either primary or secondary SS. To fulfill the ocular dryness criteria for diagnosis of SS, objective signs/symptoms must include either a Schirmer's test with a specific outcome or a Rose Bengal staining test, specifically 1) a Schirmer's test less than 8 mm wetting per 5 minutes and/or 2) a positive Rose Bengal or fluorescein staining of cornea and conjunctiva. Dr. Fox also lists 2 objective measures for dry mouth, including 1) decreased parotid flow rate using Lashley cups or other methods and 2) Abnormal biopsy of minor salivary gland (focus score of ≥ 2 based on average of 4 evaluable lobules). However, the sponsor's protocol for these trials did not include objective measures of tear flow for the purposes of screening for inclusion into the trials. Salivary flow was measured, although an acceptable value was never stated in the inclusionary criteria, and a minor salivary gland biopsy was an optional measure of Sjögren's syndrome in the inclusion criteria of both trials.

The dry eye and dry mouth inclusion criteria listed in the protocols of both pivotal trials were based upon response on a visual analogue scale to the following statements:

Eyes: "Rate the severity of your overall eye discomfort during the past 7 days. In considering your eye discomfort include pain, burning, stinging, dryness and the feeling of a foreign body in the eye. The left end of the scale, described as "Very Uncomfortable", indicates that the symptoms are very bothersome to you and noticeably interfere with your activities."

Mouth: "According to your best recollection, how dry is your mouth now, compared to

when you felt normal. In answering this question, you may wish to recall specific examples from when you were much younger."

The investigators were instructed to enroll only potential subjects who scored below the top quartile; i.e., placed a mark between 0 mm and 75 mm along the 100 mm length line on which the 0 mm point states "very uncomfortable," in the eye question, and "very dry" in the mouth question; and the 100 mm mark states "comfortable" in the eye question, and "not dry" in the mouth question.

Although this question is an attempt to verify that the potential SS subjects have dry eyes and dry mouth, it is highly subjective, and unclear why the 75% mark on the VAS was chosen as an acceptable cutoff. Even if this entrance criterion is demonstrative of dry mouth and dry eyes, the protocols are vague about the other diagnostic criteria for SS used. As discussed, objective endpoints for dry eyes and dry mouth were not used for screening purposes to enroll subjects in the pivotal trials. The question of which definition was used to diagnosis SS in the enrolled subjects then arises. Because there were a total of 28 sites used for both trials, leaving the definition of SS to each investigator has the potential to provide inconsistent, and invalid results. The sponsor stated that one of the challenges in doing research for this indication is that there is no single well-defined diagnostic set of criteria for Sjögren's syndrome (Amendment 12, December 19, 1997). In Dr. Fox's chapter, he concurs, stating, "One major problem in describing the clinical spectrum of SS is that there is no uniformly accepted definition for this syndrome." Dr. Fox points out that the differential diagnosis of primary SS is often difficult, particularly in the older patient, in whom dry eyes and dry mouth is common and probably a consequence of aging rather than the result of a systemic autoimmune process.

The sponsor states that the European criteria do not specifically require objective measures of xerophthalmia to diagnosis Sjögren's syndrome. (Refer to Appendix 1 of this review for the European Criteria : "Criteria for the Classification of Sjögren's Syndrome") However, the sponsor's protocol does not state that those are the criteria that were used for enrollment of subjects. The sponsor performed and submitted a *post hoc* analysis demonstrating that the majority of patients (580/629; 92.2%) entered into their SS studies meet the European criteria of definitive SS (4 of the 6 criteria).

A question was posed to the medical officer/rheumatologist consultant from HFD-550 (Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products) about the accurate identification and recruitment of patients with Sjögren's syndrome into these trials based upon the criteria given. The consulting medical officer concurs with the sponsor that the "European" criteria (Vitali C, et al.: *Preliminary criteria for the classification of Sjögren's syndrome-Results of a prospective concerted action supported by the European community*. Arthritis Rheum. 36: 340-347, 1993) is acceptable. In fact, the European criteria have recently been adopted by the American College of Rheumatology. A score of three is accepted as "probable primary SS" and a score of 4 may be used to establish a definitive diagnosis of

primary SS.

It 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. In order that the prescribing physician or dentist may more easily identify the patient population appropriate for the new indication, the criteria which were used in the diagnosis of SS in the subjects enrolled in the pivotal trials for this drug should be stated. It is therefore recommended that the label include the definition of SS (Vitali et al) by which subjects in the clinical trials were judged.

As was noted in the Introduction section of this review, Sjögren's syndrome may be primary or secondary, depending upon the presence of another autoimmune disorder. Although the European criteria that the sponsor cites describe primary SS, the sponsor does not discuss in this submission whether the subjects enrolled represent primary SS subjects only. The fact that 18% of the enrolled subjects in 92-01 had rheumatoid arthritis may support secondary SS, but this is not conclusive. In all likelihood, the presence of rheumatoid arthritis may be a proxy for milder SS, which may also explain the better response of this subgroup to a 2.5 mg dosing. The second pivotal trial did not stratify the groups by rheumatoid arthritis status. Although it is unknown if Salagen may have a different effect on subjects with primary or secondary SS, the sponsor did not distinguish in the inclusionary criteria of the trials between primary or secondary SS. As a result, both subjects were enrolled, fulfilling the requirement for the general labeling of SS, without specifying primary or secondary.

The subjective questions were the sponsor's way of verifying the xerophthalmia and xerostomia that must be present in patients diagnosed with SS. Although the sponsor may have employed the VAS screen to eliminate those SS subjects with mild xerostomia or xerophthalmia that does not require pharmacotherapy, the screening question did not succeed at this task. The sponsor listed "diagnosis with SS" as an inclusion criteria, which already includes xerostomia and xerophthalmia as a part of its basic definition. As would be expected, 97% of the subjects screened subjectively scored themselves as in the lower 75% of the dryness scale, which simply supports that their mouth and eyes felt dry. Because no correlation is made between the subjects's subjective view of dryness and objective measures, it does not strongly support the diagnosis. Neither does it support the notion that the sponsor has removed the mild SS subjects. Although the first protocol screened subjects for salivary flow with a demonstration of flow required for enrollment, the second trial eliminated this procedure, effectively enrolling subjects with no minimum requirement for salivary production. Therefore, the sponsor has not placed any restrictions on the severity of SS for this drug. Differences in the effect of Salagen on subjects with various forms and severity of SS would be valuable information to obtain in the future, however. One of the recommendations that resulted from this review is that the sponsor consider additional testing in the future to support various doses for differing severity of disease (See *Recommended Regulatory Action*

section of this review).

In Appendix C to protocol 92-01, entitled "Diagnostic Criteria for Sjögren's Syndrome", only two are listed as requirements - 1) dry mouth, and 2) presence of autoantibodies (to SS-A and/or SS-B and/or Rheumatoid Factor, and/or ANA) and/or a positive labial biopsy. It is of note that dry eyes are not listed here, although it was a requirement in the inclusion criteria for the trial. In Appendix D to protocol 92-02, also entitled "Diagnostic Criteria for Sjögren's Syndrome", only one is necessary - presence of autoantibodies (to SS-A and/or SS-B and/or Rheumatoid Factor, and/or ANA) and/or a positive labial biopsy. It is of particular note that neither dry eyes, nor dry mouth are listed as diagnostic criteria for SS. In a follow-up telephone conversation with the sponsor on December 4, 1997 (see minutes for details), the sponsor explained that appendix D contained a typographical error. Fortunately, the inclusionary section of each trial's protocol lists dry mouth and dry eyes.

Orphan Drug Status

The preceding discussion concerning the definition of SS raises a concern when one reviews the sponsor's application for Orphan Drug status (Date of submission: 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 discussion with Dr. 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.

Safety

From the outset, it must be stated that the safety of Salagen at a greater dose 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 being 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.

Adverse experience data were presented from the two pivotal trials, as well as 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. None of the serious adverse events reported were determined to be related to the pilocarpine.

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.

Proposed Labeling

This section of the review contains two subsections. The first is a revision of the sponsor's proposed label, in which strikeout is used for deletions of the sponsor's proposed text, and redline for agency additions. The second section is an unmarked version of the final approved labeling. All of these changes were made to the sponsor's proposed label to more accurately reflect what the sponsor has demonstrated in this NDA submission.

Redacted 21

pages of trade

secret and/or

confidential

commercial

information