21079

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021079

Trade Name: ALAMAST 0.1%

Generic Name: PEMIROLAST POTASSIUM OPHTHALMIC SOLUTION

Sponsor: SANTEN INCORPORATED

Approval Date: 09/24/1999

INDICATION(s): PREVENTION OF ITCHING OF THE EYE DUE TO ALLERGIC CONJUNCTIVITIS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION for: 021079

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter			X	
Approvable Letter			X	
Final Printed Labeling			X	
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)	X			
Statistical Review(s)			X	
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)			X	
Administrative Document(s)/ Correspondence	X			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-079

SEP 24 1999

Santen Incorporated
Attention: Merwin Jerry Hansen
Chief Executive Officer
555 Gateway Drive
Napa, CA 94558

Dear Mr. Hansen:

Please refer to your new drug application (NDA) dated March 25, 1999, received March 26, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alamast (pemirolast potassium ophthalmic solution), 0.1%.

We acknowledge receipt of your submissions dated March 26, April 23 and 28, May 12 and 18, June 14, 21, 25 and 29, July 14 (two), 15, 22, 23 (two) and 28, August 4, 5, 11, 12, and 25, and September 9, 20, and 23, 1999.

This new drug application provides for the use of Alamast (pemirolast potassium ophthalmic solution), 0.1% for the prevention of itching of the eye due to allergic conjunctivitis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling text submitted September 23, 1999. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical in content to the submitted package insert dated September 23, 1999. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 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 NDA 21-079." Approval of this submission by FDA is not required before the labeling is used.

We remind you of the Phase 4 commitment specified in your submission dated September 20, 1999. This commitment is for the submission of the full testing results for the next 6 production batches of both the drug substance and the drug product. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Raphael R. Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 24 September 1999

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-079
Original

NDA 21-079
Medical Officer's Review

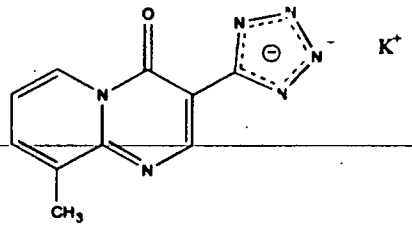
Submission: 3/25/99
Review Completed: 7/19/99

Proposed Tradename: Alamast

Generic Name: Pemirolast potassium ophthalmic solution, 0.1%

Chemical Name: 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-*a*]pyrimidin-4-one, potassium salt

4H-pyrido[1,2-a]pyrimidin-4-one,9-methyl-3-(1H-tetrazol-5-yl)-potassium



Chemical Structure – Formula $C_{10}H_7KN_6O$

Sponsor: Santen Incorporated
555 Gateway Drive
Napa, CA 94558

Pharmacologic Category: Mast cell stabilizer

Proposed Indication: Prevention and relief of ocular itching due to allergic conjunctivitis

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

NDA Drug Classification: 1P

Related IND: IND [redacted]

2 **Table of Contents**

3 **Material Reviewed**

NDA 21-079 Volumes 1.33-1.54

4 **Chemistry/Manufacturing Controls** – See Chemistry Review

Table 1
Quantitative Composition

Ingredient	Quantity (mg/mL)	Percent (w/v)
Pemirolast potassium		
Lauralkonium chloride		
Glycerin		
Dibasic sodium phosphate		
Monobasic sodium phosphate,		
Sodium hydroxide		
Phosphoric Acid		
Purified water		

1 page
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TRADE Secret
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Commercial

6 Clinical Background

Allergic conjunctivitis is one of the most common forms of ocular allergy. Sensitive individuals develop ocular manifestations such as injection, itching, chemosis, discharge, and tearing after exposure to airborne antigens. These responses are caused by a number of preformed allergic mediators (histamine, chemotactic factors, etc.) that are released during mast cell degranulation. The release of these mediators also triggers a secondary cascade of chemical agents to produce newly formed mediators such as leukotrienes and prostaglandins.

Pemirolast potassium is a mast cell stabilizer that inhibits the *in vivo* Type I immediate hypersensitivity reaction.

6.1 Relevant Human Experience

Allergic conjunctivitis has been treated effectively with topical agents such as decongestants, antihistamines (or their combinations), mast cell stabilizers, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs).

There are no mast cell stabilizers currently marketed in the United States for the treatment of allergic conjunctivitis.

6.4 Foreign Experience

The following formulations of pemirolast potassium are commercially available in foreign countries (see below).

Country	Date Approved	Formulation
Japan	1991	10 mg tablets for bronchial asthma and allergic rhinitis
	1992	Dry syrup for bronchial asthma
	1994	5 mg tablets for bronchial asthma and allergic rhinitis
	1995	0.1% ophthalmic solution for allergic and vernal conjunctivitis
China	1996	0.1% ophthalmic solution for allergic and vernal conjunctivitis
Korea	1998	0.1% ophthalmic solution for allergic and vernal conjunctivitis

The 5 and 10 mg tablets, and the dry syrup formulation are marketed in Japan by Tokyo Tanabe and Bristol-Myers Squibb K.K. under the trade names Alegysal® and Pemilaston,® respectively. The 0.1% ophthalmic solution is marketed by Santen Ltd. and Bristol-Myers Squibb K.K. under the trade names Alegysal® and Pemilaston,® respectively, and is the same formulation proposed for approval under this NDA.

The drug has not been withdrawn from marketing in any country for any reason related to safety or effectiveness. There are no pending foreign marketing applications for this drug.

6.4 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics – See Pharmacology Review

7 Description of Clinical Data Sources

Included in this medical officer's review are the following five clinical trials conducted in the United States under IND 49,936:

- Three Phase III environmental studies with prophylactic dosing in adult ocular allergy patients (Study 02-002 conducted in Allergy Season 1996) and ocular allergy patients at least 10 years of age (Studies 02-003 and 02-004 conducted simultaneously in Allergy Season 1997)
- A Phase II dose-response study in adult ocular allergy patients to assess the optimal concentration of TBX (Study 02-001)
- A Phase I safety study in healthy children three to five years of age (Study 02-005)

See Clinical Data Sources, Table 3.

Table 3
Clinical Data Sources

Study No.	Investigator (Location) Start Date (Study Status)	Study Design/ Patient Population	Treatment doses, frequency and duration	Patients entering / receiving / completing treatment	Age Range (mean)	Sex M/F (%)	Race B/W/O (%)	Irides Light/Dark (%)
Phase 3 U. S. Controlled Clinical Studies								
02-002	Abelson (US) Aug. 1996 (Completed)	Randomized, triple-masked, parallel-group, placebo-controlled, single-center in adult patients with a history of allergy and a positive CAC response	0.1% TBX Placebo q.i.d. x 11 wks	60/59/52 60/60/56	18-66 (38.7)	53/47	4/95/1	45/55
02-003	Berdy, Parver, Greiner, Crampton (US) Aug. 1997 (Completed)	Randomized, double-masked, parallel-group, placebo-controlled, multi-center in patients ≥ 10 years of age with a history of allergy and a positive CAC response	0.1% TBX Placebo q.i.d. x 12-16 wks	71/70/65 72/69/62	10-66 (35.1)	46/54	15/82/3	57/43
02-004	Mundorf, John, Lonsdale (US) Jul. 1997 (Completed)	Randomized, triple-masked, parallel-group, placebo-controlled, multi-center in patients ≥ 10 years of age with a history of allergy and a positive CAC response	0.1% TBX Placebo q.i.d. x 15-17 wks	67/65/57 64/64/49	12-64 (36.1)	50/50	11/87/2	61/36

Table 3
Clinical Data Sources

Study No.	Investigator (Location) Start Date (Study Status)	Study Design/ Patient Population	Treatment doses, frequency and duration	Patients entering / receiving / completing treatment	Age Range (mean)	Sex M/F (%)	Race B/W/O (%)	Irides Light/Dark (%)
Phase 2 U. S. Controlled Clinical Study								
02-001	Abelson (USA) Mar. 1996 (Completed)	Randomized, triple-masked, contralateral-eye comparison, placebo-controlled, single-center in adults with a history of allergy and a positive CAC response.	0.1% TBX/ Placebo 0.25% TBX/ Placebo b.i.d. x 14 days (prior to CAC)	60/60/57 58/58/55	18-62 (36.1)	48/52	1/99/0	68/32
Phase 1 U.S. Controlled Clinical Study								
02-005	Rubin (USA) Oct. 1997 (Completed)	Randomized, double-masked, parallel-group, placebo-controlled, single-center in healthy children with asymptomatic eyes.	0.1% TBX or Placebo q.i.d. x 6 wks	20/20/17 10/10/9	3-5 (4.0)	63/37	3/37/60	---/---

Demographic information (age, sex, race, and iris color) is presented for evaluable subjects.

Note: Light iris color includes green, blue, and hazel irides; and dark iris color includes black and brown irides. Studies 02-003 (Study 1997a) and 02-004 (Study 1997b) were conducted simultaneously during Allergy Season 1997.

TBX = Pemirolast potassium
CAC = Conjunctival allergen challenge
M/F = Male/Female
B/W/O = Black/White/Other
--- = Data not available

8 Clinical Studies

8.1.1 Study #1 Protocol 02-002

Title: A prospective, randomized, triple-masked, parallel-group, single-center comparison trial of the ocular efficacy and safety of 0.1% pemirolast potassium ophthalmic solution with that of placebo in subjects with allergic conjunctivitis

Objective: The objective of this trial was to compare the efficacy and safety of 0.1% pemirolast potassium ophthalmic solution with placebo (vehicle) when administered bilaterally four times daily (QID) for approximately 6-12 weeks (depending on the length of the allergy season) in treating the ocular signs and symptoms associated with allergic conjunctivitis.

Study Design: A prospective, randomized, triple-masked, parallel-group, single-center study comparing 0.1% pemirolast with placebo (vehicle) used prophylactically in subjects with a history of allergic conjunctivitis. Study duration was 11 weeks.

Test Drug Schedule: Subjects instilled 1-2 drops of either pemirolast 0.1% or vehicle four times a day (QID) in each eye beginning at Visit 1 and continuing until 5-30 days after the first killing frost (Visit 4).

In addition, the investigator or his trained designee administered 1-2 drops of study medication in each of the subject's eyes 20 ± 1 minutes prior to allergen challenge at Visit 4.

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Mark B. Abelson, MD (003) [redacted] 863 Turnpike Street North Andover, MA 01845 (978) 685-8900	120	501-620	18 Aug 1996	1 Nov 1996	11 weeks

8.1.1 Study Design

This was a prospective, randomized, triple-masked, parallel-group, single-center study comparing 0.1% pemirolast with placebo (vehicle) used prophylactically in subjects with

a history of allergic conjunctivitis. 120 subjects were enrolled in order to obtain 108 completed subjects.

Visit 1 (Day 0, Baseline) occurred prior to the start of the ragweed pollen season. Prospective subjects who gave written informed consent and met required entry criteria underwent a conjunctival allergen challenge (CAC) titration procedure with ragweed. This titration procedure involved bilateral instillation of progressively greater concentrations of ragweed antigen to determine the final concentration necessary to provoke a positive response in both eyes [(2+ itching and (2+ redness in at least one of the three vessel beds (ciliary, episcleral, or conjunctival)]. Qualified subjects were enrolled, and randomly assigned to receive either 0.1% pemirolast or placebo. Subjects instilled 1-2 drops of masked study medication four times a day (QID) in each eye beginning on Day 1 and continuing until 5-30 days after the first killing frost (Visit 4). During the study, subjects recorded their ocular itching and redness in a diary each day at bedtime starting on Day 1 and continuing until 1-5 days after Visit 4 (Visit 5).

The study duration was to be approximately 6-12 weeks, depending on the length of the ragweed allergy season and occurrence of the first killing frost. The first killing frost was defined as a frost that was sustained through two or more hours below 32 °F (0 °C). The killing capacity specifically for ragweed was confirmed by ragweed pollen counts of zero (0) grains per cubic meter. Subjects returned for four scheduled follow-up visits: Day 7± 2 (Visit 2), Day 28 (3 ±Visit 3), 5-30 days after first killing frost (Visit 4), and 1-5 days after Visit 4 (Visit 5). In addition, subjects were contacted by telephone each week during those weeks that did not include a scheduled office visit.

Ophthalmic evaluations were performed at baseline and each scheduled follow-up visit, and included best-corrected visual acuity (Snellen), slit-lamp examination (biomicroscopy), and ocular signs and symptoms. In addition, fundus examinations (ophthalmoscopy) and IOP measurements were performed at Visits 1 and 5.

At Visit 4, subjects received 1-2 drops of study medication in each eye 20 ± 1 minutes prior to undergoing a second CAC with the same concentration of ragweed antigen that provoked a positive response at Visit 1. Post-challenge ocular signs and symptoms were recorded at 3, 10, and 20 minutes after challenge. Photographs of each eye were also taken after the 10-minute post-challenge assessment. Subjects were exited from the study at Visit 5.

Study Medications

Study medications were supplied in 10 cc bottles with a 10 mL fill, and were shipped to the investigator labeled with the subject number, the protocol number, and storage instructions. The following lots of investigational products were used in this study:

- 0.1% pemirolast potassium ophthalmic solution containing 0.1% pemirolast potassium, lauralkonium chloride (LAK) 0.005%, glycerin, monobasic sodium

phosphate, dibasic sodium phosphate, phosphoric acid and/or sodium hydroxide (adjust pH), and purified water (Formulation No. 1008S, Lot No. 6A9001)

- Vehicle of pemirolast potassium ophthalmic solution (placebo) containing lauralkonium chloride (LAK) 0.005%, glycerin, monobasic sodium phosphate dibasic sodium phosphate, phosphoric acid and/or sodium hydroxide (adjust pH), and purified water (Formulation No. 1007S, Lot No. 6B0001)

Study Masking

This study used a triple-masked design, where the identities of the study medications were concealed from the subject, the investigator, and the Sponsor's monitors and clinical research personnel. During the study, no study medication was unmasked.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

To be eligible for participation in this study, subjects were required to meet all of the following criteria:

- Ocular health within normal limits with the exception of a history of allergic conjunctivitis
- Willing to avoid disallowed medications during the study period; disallowed medications included steroids, antihistamines, mast cell stabilizers, NSAIDs, newly instituted immunotherapy, immunosuppressive agents, all topical ocular preparations, and any medication that the investigator felt could interfere with the study parameters
- Willing to discontinue contact lens wear at least 72 hours prior to Visit 1, and agreed not to wear contact lenses for the duration of the study
- Women of childbearing potential must have been using reliable contraceptive methods [chemical contraceptives (oral, implantable, or injectible), spermicide with barrier, or IUD] throughout the study, and must have had a negative urine pregnancy test prior to enrollment into this study
- 18 years of age or older
- Either sex and any race
- Willing to follow instructions and able to make all required study visits
- Willing to give written consent
- History of allergic conjunctivitis, and a positive skin-prick test with ragweed antigen within the past two years
- Positive reaction to ragweed antigen challenge in both eyes [(2+ itching and (2+

redness in at least one of the three vessel beds (ciliary, episcleral, or conjunctival)] at Visit 1 (Day 0, Baseline)

Exclusion Criteria

Subjects with any of the following conditions were excluded from participating in the study:

- Females who were lactating, pregnant, or were planning a pregnancy; not using adequate birth control per inclusion criteria; or not surgically sterile
- Using any systemic medication which may have interfered with the study: MAO inhibitors, nonsteroidal anti-inflammatory agents (e.g., aspirin, ibuprofen), mast cell stabilizers, antihistamines, or steroids should have been discontinued 72 hours before the study and not used during the study
- Presence of any significant illness that could be expected to interfere with the study, particularly any autoimmune disease such as rheumatoid arthritis which can be associated with dry eye syndrome
- Regular use of topical ophthalmic solutions during the study, including tear substitutes, or use of any topical ophthalmic medication less than one week before the study
- Subjects using ophthalmic medications that required longer than a one-week washout were not included in the study
- Use of any oral/topical investigational drug or device within 30 days before receipt of study medication
- Ocular surgery within 6 months before the beginning of the study
- History of uncontrolled cardiovascular, hepatic, and/or renal disease
- History of allergy or sensitivity to any mast cell stabilizer or to any component of the study medication, including the preservative
- Current alcohol and/or drug abuse
- History of retinal detachment, diabetic retinopathy, or any retinal disease which may be progressive during the time course of the study
- External ocular disease, inflammation or infection of the eye and/or eyelids
- History of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome
- Subjects with only one sighted eye or not correctable to 20/80 in both eyes
- Stable immunotherapy for less than 3 months prior to the initiation of the study
- Evidence of signs and/or symptoms of allergic conjunctivitis [i.e., >0.5+ itching and/or >1+ redness in any of the three vessel beds (ciliary, episcleral, or conjunctival)] at the pre-challenge examination at Visit 1

In addition, the investigator could have declared any subject ineligible for any sound medical reason.

The use of any prescription or over-the-counter medication during the study or within 30 days of entering the study was noted on the subjects' CRFs, including start and stop +dates, dosing regimen, and indication. Treatment necessary for a subject's welfare that did not interfere with the response to study medication was permitted at the discretion of the investigator.

The following concomitant medications were prohibited prior to and/or during the study:

- Any systemic steroids, antihistamines, mast-cell stabilizers, nonsteroidal anti-inflammatory agents (e.g., aspirin, ibuprofen), or monoamine oxidase inhibitors during the study period or within 72 hours of entering the study [Note that histamine H_2-receptor antagonists (e.g., famotidine, cimetidine) and up to 162 mg per day of aspirin were allowed]
- Any topical ophthalmic solutions, including tear substitutes, during the study period
- Any topical ophthalmic medications within one week of entering the study
- Any ophthalmic medication requiring longer than a one-week washout period
- Use of any oral/topical investigational drug or device during the study period or within 30 days before receipt of study medication
- Use of stable immunotherapy for less than 3 months prior to entering the study

The decision to administer a prohibited medication was done with the safety of the study participant as the primary consideration.

Efficacy Variables

The primary efficacy variables in this study were daily ocular itching and redness recorded in the subject diary, and ocular itching and redness recorded at the office visits.

Daily Ocular Itching and Redness from Subject Diary:

The following subject diary variables were evaluated using 9-point scales (0-4 scale with half-grades allowed).

- Worst Itching During the Day
  Each day at bedtime during the study period, subjects evaluated their worst ocular itching episode during the day using the following 9-point scale (0-4 scale with half-grades allowed):

  0 None

  1+ A tickling sensation involving more than just the corner of the eye

2+ A mild, continuous itch not requiring rubbing. This itch may be localized (i.e., involving just the corner of the eye)

3+ A severe itch which you would like to rub (but do not, as it would jeopardize the study and exacerbate your symptoms)

4+ An incapacitating itch which would require significant eye rubbing (but do not, as it would jeopardize the study and exacerbate your symptoms)

- Bedtime Itching
  Each day at bedtime during the study period, subjects evaluated ocular itching using the same 9-point scale as described above.
- Bedtime Redness
  Each day at bedtime during the study period, subjects evaluated ocular redness using a 9-point scale (0-4 scale with half-grades allowed). Each subject diary contained the same set of color photographs displaying examples of 0, 1+, 2+, 3+, and 4+ ocular redness.

Ocular Itching and Redness at Study Visits:

The following pre-challenge and/or post-challenge ocular itching and redness variables were evaluated at each study visit using 9-point scales (0-4 scales with half-grades allowed).

- Ciliary Injection
- Episcleral Injection
- Conjunctival Injection
- Maximum Redness
  The maximum redness score was calculated using the greatest score among ciliary, episcleral, and conjunctival injection
- Itching
  Subjects evaluated ocular itching using the same 9-point scale as described above.

Ocular itching and redness were evaluated at each study visit, and included the pre-challenge evaluations obtained at Visit 1 (Day 0, Baseline) and Visit 4 (5-30 days after the first killing frost), in addition to the evaluations obtained at follow-up visits without a CAC [Visit 2 (Day 7), Visit 3 (Day 28), and Visit 5 (1-5 days after Visit 4)].

Secondary Efficacy Variables

Secondary efficacy variables included the following pre-challenge and/or post-challenge ocular signs and symptoms. Variables were evaluated at each study visit using 9-point scales (0-4 scales of increasing severity with half-grades allowed).

- Chemosis
- Lid Swelling

- Tearing

Ocular signs and symptoms were evaluated at each study visit, and included the pre-challenge evaluations obtained at Visit 1 (Day 0, Baseline) and Visit 4 (5-30 days after the first killing frost), in addition to the evaluations obtained at follow-up visits without a CAC [Visit 2 (Day 7), Visit 3 (Day 28), and Visit 5 (1-5 days after Visit 4)].

Other Study Variables

Each day at bedtime during the study period, subjects evaluated their exposure to the outdoors (Ragweed pollen) using a 3-point scale (0-2 scale).

Safety Variables

This study included the following safety variables:

- Adverse Events
  Subjects were queried at each follow-up visit and telephone contact regarding occurrence of any adverse events. Adverse event information included a description of the event, onset, severity, treatment required, outcome, and relationship to use of the study medication.
- Visual Acuity
  Best-corrected visual acuity was measured at each study visit using a standard Snellen chart, and recorded in English units (e.g., 20/20). For the purpose of analysis, English units were converted to ETDRS logMAR scoring units.
- Slit-Lamp Examination (Biomicroscopy)
  A biomicroscopic evaluation was performed at each study visit, and included the lids, conjunctiva, anterior chamber, cornea, tear meniscus, and lens. Variables were graded as normal or clinically significantly abnormal.
- Intraocular Pressure
  IOP was measured in mm Hg at baseline (Visit 1) and the exit visit (Visit 5).
- Fundus Examination (Ophthalmoscopy)
  An undilated ophthalmoscopic evaluation was performed at baseline (Visit 1) and the exit visit (Visit 5), and included the vitreous (graded on a 4-point scale: 0-3); the retina, macula, choroid (graded on a 3-point scale: 0-2); and the optic nerve (graded on a 4-point scale: 0-3).

Table 4
Schedule of Visits and Measurements

Procedures	VISIT 1 Day 0, Baseline		VISIT 2	Telephone Contact 1	Telephone Contact 2	VISIT 3	Telephone Contact 3 [1]	VISIT 4 5-30 Days after First Killing Frost		VISIT 5 1-5 Days after Visit 4
	Pre-CAC	Post-CAC	Day 7 ± 2	Day 14 ± 3	Day 21 ± 3	Day 28 ± 3	Day 35 ± 3	Pre-CAC	Post-CAC	
Informed Consent	X									
Medical History	X		X	X	X	X	X	X		X
Pregnancy Test	X									
Skin Prick Test	X									
Visual Acuity	X		X			X		X		X
Slit-Lamp Exam	X		X			X		X		X
Allergic Evaluation	X	X [2]	X			X		X	X [3]	X
Investigator Instill Drug								X [4]		
CAC (Ragweed)	X [5]							X [6]		
Photographs									X [7]	
Instill Relief Medication [8]		X							X	
IOP		X								X
Fundus Exam (Undilated)		X								X
Dispense Drug		X				X [9]				
Dispense Diary		X								
Diary Review/Record			X			X		X		
Diary Review/Collect										X
Collect Drug								X		
Exit Form										X

[1] Additional telephone contacts conducted prior to Visit 4 if necessary.
[2] Post-CAC allergic evaluation performed 10 minutes after challenge.
[3] Post-CAC allergic evaluations performed at 3, 10, and 20 minutes after challenge.
[4] Study medication administered 20 minutes prior to CAC.
[5] Determined allergen dose necessary to induce ≥2+ ocular redness and itching OU.
[6] Used the same allergen dose that induced ≥2+ ocular redness and itching OU at Visit 1.
[7] Photographs of each eye were taken after the 10-minute post-challenge assessment.
[8] Approved topical ocular antihistamine/vasoconstrictor administered in each eye if necessary.
[9] Dispensed additional study medication if necessary.

Changes in Planned Analyses

Originally the data were to be analyzed to determine if there was: 1) a statistically significant difference in the percentage of subjects (0.1% pemirolast vs. placebo) whose condition did not worsen from their baseline post-challenge measurements (≤0.5 units worsening); 2) a statistically and clinically (≥1 unit) significant mean change from baseline in post-challenge measurements; and 3) a statistically significant difference (active vs. placebo) in the percentage of allergic episodes (combined itching and redness score of (2+) as reported daily in subject diaries.

However, treatment success, rather than treatment failure, was considered a more appropriate analysis since the objective of this study was to determine the efficacy of 0.1% pemirolast in preventing ocular signs and symptoms associated with allergic conjunctivitis. Prevention of ocular itching and redness was assessed by calculating the daily percent of subjects with a score of zero in both eyes for each of worst itching during the day, bedtime itching, and bedtime redness.

Subject Disposition and Demographics

One hundred twenty (120) subjects were enrolled in the study by one investigator, with 90% (108/120 subjects) completing the study as planned. The first subject was enrolled on August 18, 1996. The last subject exited the study on November 1, 1996.

Ten percent (10%, 12/120) of the subjects were discontinued early: 13% (8/60 subjects) in the 0.1% pemirolast group and 7% (4/60 subjects) in the placebo group. There was no statistically significant difference between treatment groups in the discontinuation rate. Reasons for discontinuation included: seven subjects due to improper entry, three subjects due to subject decision, one subject due to an adverse event (a severe anaphylactic reaction), and one subject due to non-compliance (missed visits).

Table 5
Subject Disposition

	Pemirolast		Placebo		Total		P-Value
	N	%	N	%	N	%	
Enrolled	60	100.00	60	100.00	120	100.00	0.361
Completed	52	86.67	56	93.33	108	90.00	
Discontinued	8	13.33	4	6.67	12	10.00	
Non-Compliance	1	1.67	0	0	1	0.83	
Subject Decision	2	3.33	1	1.67	3	2.50	
Adverse Event	1	1.67	0	0	1	0.83	
Improper Entry	4	6.67	3	5.00	7	5.93	

Table 6
Discontinued Subjects

Subject#	*Date*	*Exit Date*	*Reason*	*pemirolast 0.1%*
0506	08/18/1996	09/15/1996	Subject Decision	
0514	08/18/1996	08/18/1996	Subject Decision	
0541	08/18/1996	09/17/1996	Improper Entry	
0581	08/20/1996	08/20/1996	Improper Entry	
0585	08/20/1996	08/27/1996	Anaphylactic Rxn to Antigen	
0609	08/20/1996	09/03/1996	Improper Entry	
0612	08/22/1996	10/23/1996	Non-Compliance	
0618	08/22/1996	08/27/1996	Improper Entry	

Subject#	*Date*	*Exit Date*	*Reason*	*placebo*
0502	08/18/1996	09/15/1996	Subject Decision	
0523	08/18/1996	09/11/1996	Improper Entry	
0550	08/18/1996	09/03/1996	Improper Entry	
0576	08/20/1996	09/23/1996	Improper Entry	

There were no statistically significant differences between treatment groups for any of the medical history variables. There was also no significant between-group difference in the mean concentration of ragweed antigen needed to provoke a positive response to conjunctival allergen challenge at Visit 1.

Table 7
Demographic Information – ITT Population

	Pemirolast	Placebo	Total	P-Value
Age				
N	60	60	120	0.603
Mean	39.03	37.95	38.49	
Std	11.36	11.38	11.34	
Min	18.00	18.00	18.00	
Max	64.00	66.00	66.00	

	Pemirolast		Placebo		Total		P-Value
	N	%	N	%	N	%	
Gender							0.044
Male	26	43.33	38	63.33	64	53.33	
Female	34	56.67	22	36.67	56	46.67	
Race							1.000*
Caucasian	57	95.00	57	95.00	114	95.00	
Black	3	5.00	2	5.00	5	4.17	
Other	0	0	1	1.67	1	0.83	
Iris Color							0.141**
Dark Eyes	29	48.33	38	63.33	67	55.83	
Brown	14	23.33	26	43.33	40	33.33	
Black	15	25.00	12	20.00	27	22.50	
Light Eyes	31	51.67	22	36.67	53	44.17	
Blue	27	45.00	20	33.33	47	39.17	
Green	4	6.67	2	3.33	6	5.00	

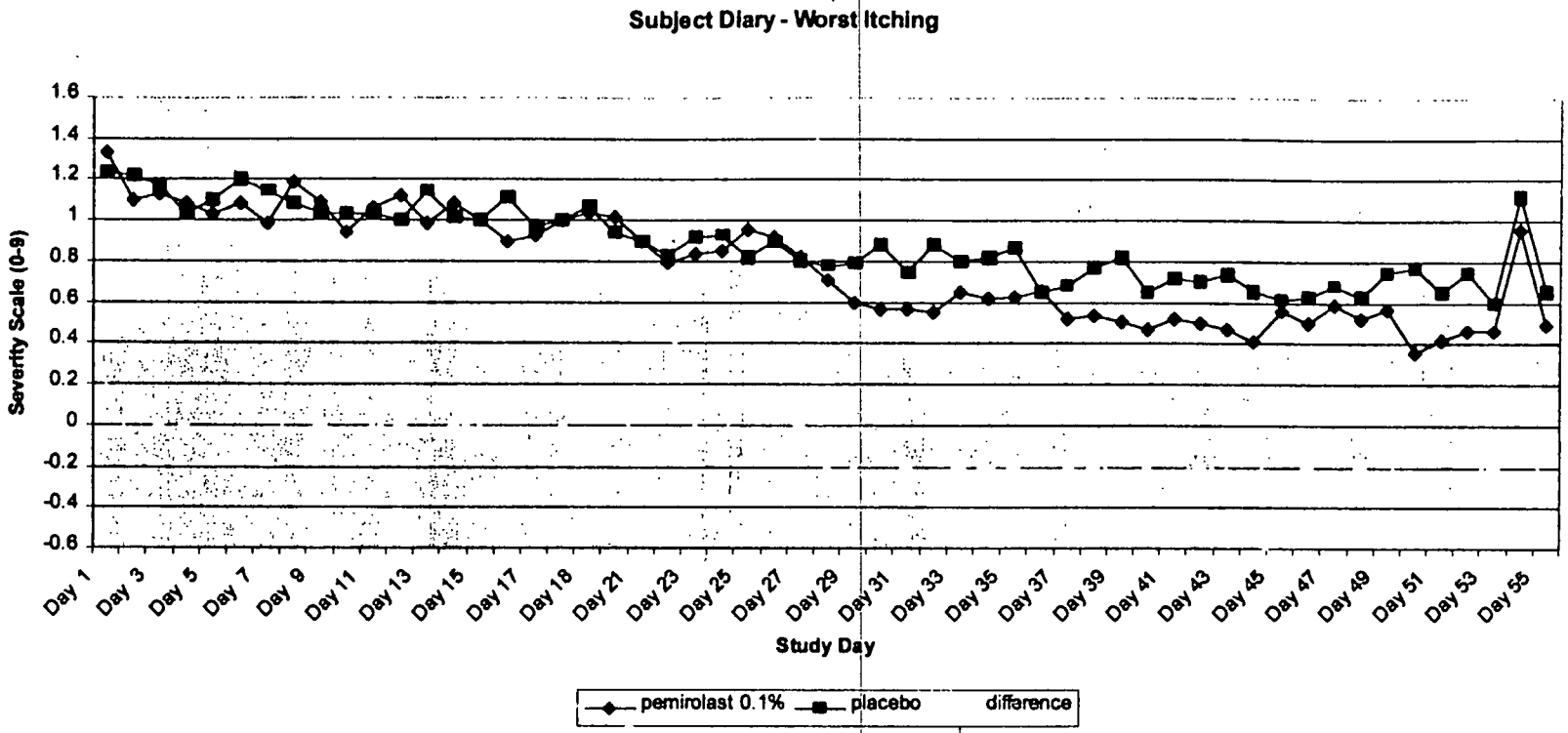
*Caucasian vs. Non-Caucasian
**Dark Eyes vs. Light Eyes

8.1.1 Efficacy – Protocol 02-002 Intent-to-Treat Population

Primary Efficacy Variables

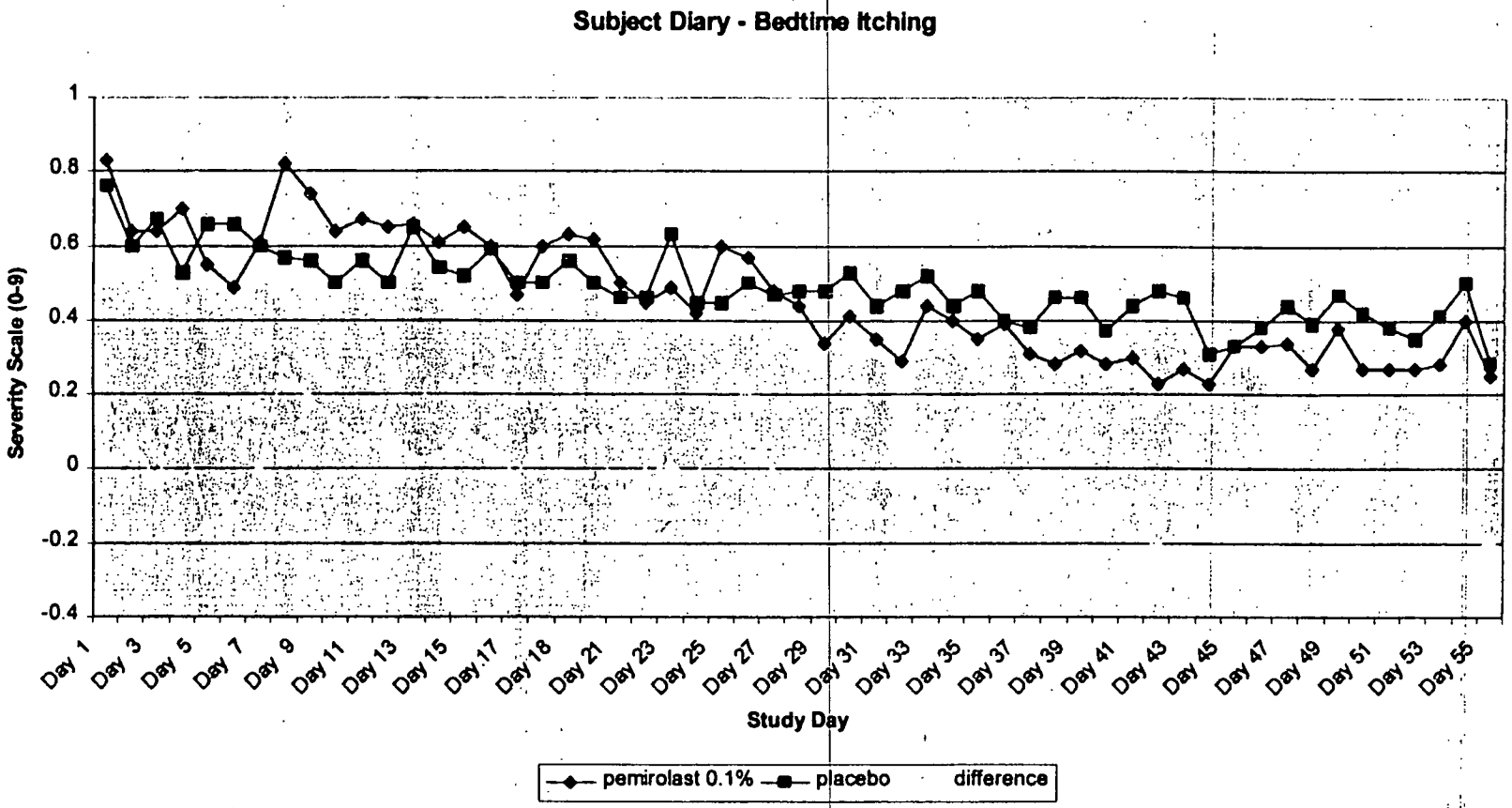
Reviewer's Comments:

A negative change on the severity scale indicates improvement.
Diary data evaluated to Day 55 – subject numbers precipitously dropped after that date



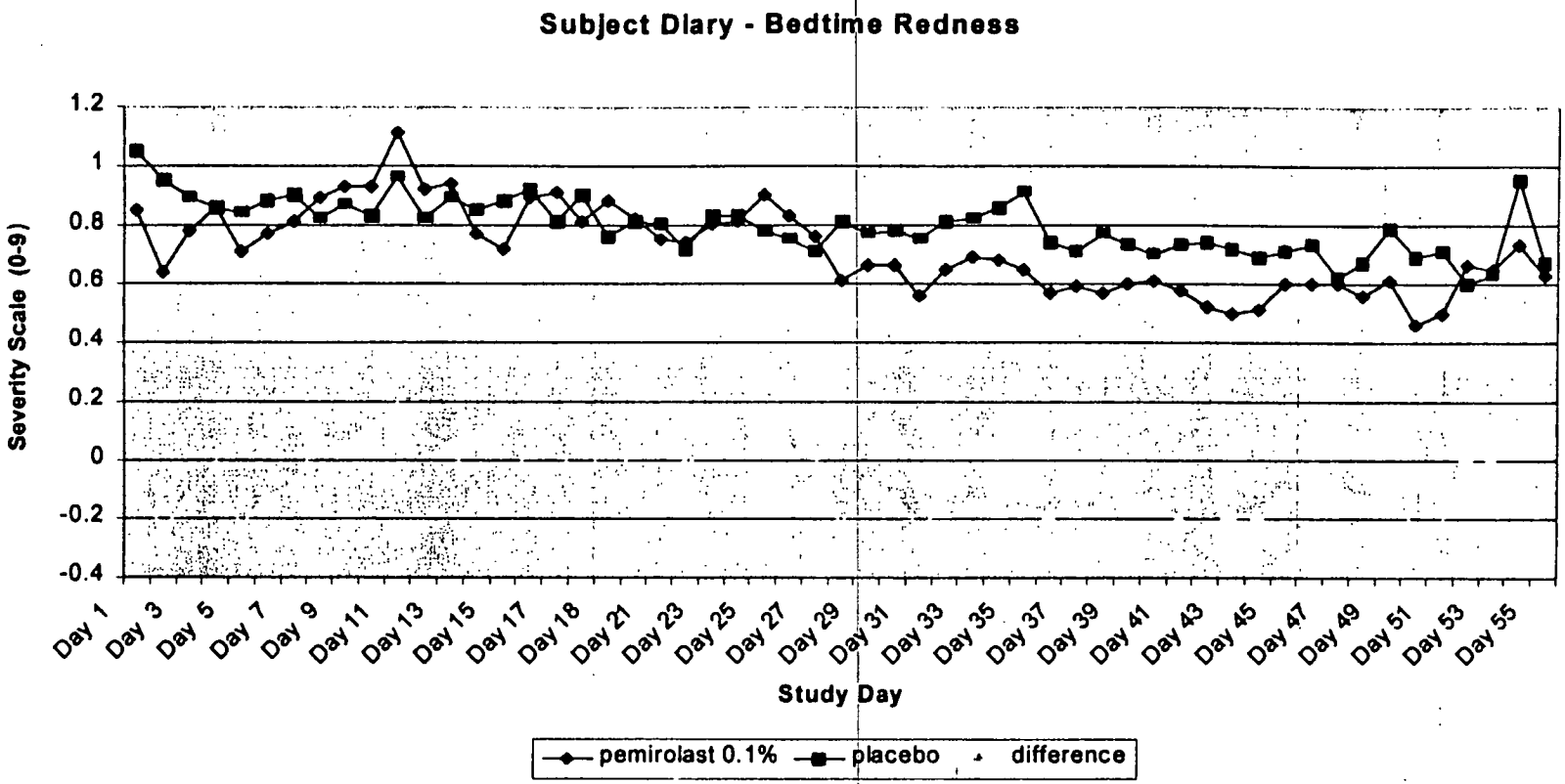
Subject Diary – Worst Itching

Worst itching during the day was lower in pemirolast-treated subjects than in placebo-treated subjects on 43 out of 55 days, with 25 days being statistically significant. The difference occurred primarily after Day 28 of treatment. For 56% (31/55) of the days, the mean difference in itching was 0.10-0.34 units lower in the pemirolast 0.1% group than in the placebo group.



Subject Diary – Bedtime Itching

Ocular itching at bedtime was lower in pemirolast-treated subjects than in placebo-treated subjects on 36 out of 55 days, with 11 days being statistically significant. The difference was most consistent after Day 28. For 42% (23/55) of the days, the mean difference in itching was 0.10-0.19 units lower in the pemirolast 0.1% group than in the placebo group.



Subject Diary – Bedtime Redness

Ocular redness at bedtime was lower in pemirolast-treated subjects than in placebo-treated subjects on 40 out of 55 days, with 18 days being statistically significant. The difference was most consistent after Day 28. For 53% (29/55) of the days, the mean difference in itching was 0.10-0.24 units lower in the pemirolast 0.1% group than in the placebo group.

Subject Diary – Worst Itching, Bedtime Itching, and Bedtime Redness: Percent of Subjects with a Score of Zero by Day

Although there were more reports of no itching and no redness in pemirolast-treated subjects than in vehicle-treated subjects, only one day (Worst Itching Diary) reached statistical significance.

Ocular Redness and Itching at Study Visits – Pre-Challenge and Post-Challenge

Although statistically significant between-group differences were seen, the difference in mean scores for these variables was never more than 0.2 to 0.45 units.

Secondary Efficacy Variables – Pre- and Post-Challenge

Although statistically significant between-group differences were seen, the difference in mean scores for these variables was never more than 0.08 units.

Outdoor Exposure to Ragweed Pollen

There were no statistically significant differences between treatment groups in subject's recorded outdoor exposure to ragweed pollen during allergy season.

8.1.1 Safety

Adverse Events

Of the 120 enrolled subjects, 70 subjects reported 149 adverse events during the study. There were no significant differences between treatment groups in overall adverse events. The incidence of adverse events was 60% (36/60 subjects) in the 0.1% pemirolast group and 57% (34/60 subjects) in the placebo group. Most adverse events were of mild-to-moderate severity. There were two serious adverse events in the 0.1% pemirolast group: one subject experienced severe repeated dislocation of the shoulder, and one subject experienced a severe anaphylactic reaction to ragweed used in the baseline skin-prick test and CAC prior to using study medication. No deaths or other significant events occurred during the study

There were no significant differences between treatment groups in the incidence of adverse events. The most frequently reported events were headache (30%, 36/120 subjects), rhinitis (25%, 30/120 subjects), cold symptoms (12%, 14/120 subjects), and back pain (4%, 5/120 subjects).

The incidence of ocular adverse events was 5% (6/120): 5% (3/60 subjects) in the 0.1% pemirolast group and 5% (3/60 subjects) in the placebo group. The most frequently reported ocular event was itching (2%, 2/60 subjects).

Table 8
Adverse Events by Body System
Reported ≥ 3%

COSTART body system/ Preferred term	pemirolast 0.1%		vehicle	
	N	%	N	%
No Adverse Event	24	40	26	43.33
BODY/GEN				
Infect	6	10.0	8	13.3
Pain	2	3.33	1	1.67
BODY/BACK				
Pain Back	0	0	5	8.33
RES/NASP				
Pharyngitis	2	3.33	1	1.67
RES/NOSE				
Rhinitis	16	36.67	14	23.33
RES/SINS				
Sinusitis	0	0	2	3.33
SS/EYE/GEN				
Itching Eye	0	0	2	3.33
UG/FG/MENS				
Dysmenorrhea	3	5.00	0	0

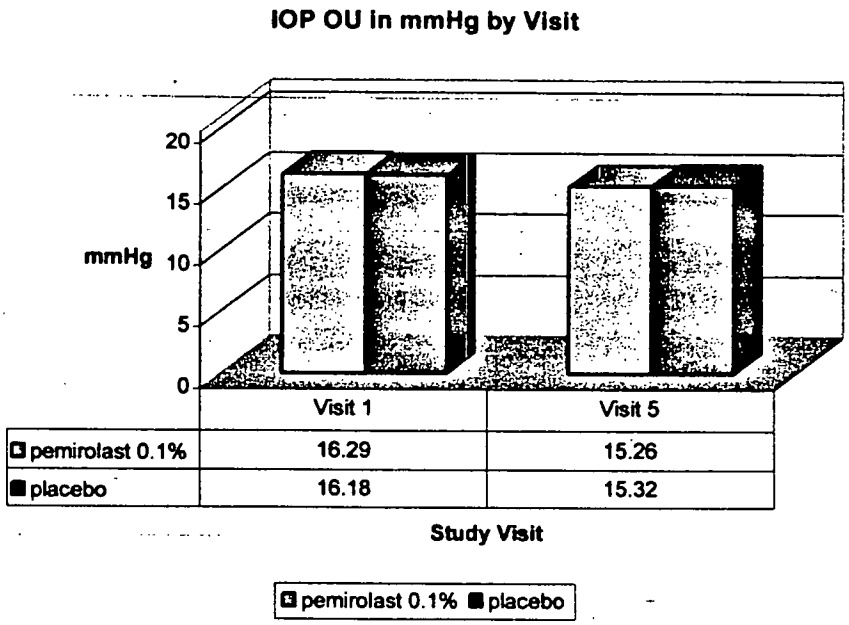
Table 9
Serious Adverse Events

Investigator/Patient	Investigator's Adverse Event Description
pemirolast 0.1%	
003-0541	Pneumonia
003-0541	Repeated Shoulder Dislocation
003-0585	Anaphylaxis
placebo	
none	none

Visual Acuity and Slit Lamp Exam

There were no statistically significant differences between treatment groups in best-corrected visual acuity (Snellen) or slit lamp exam at baseline or any follow-up visit, and no significant differences between groups in change from baseline in visual acuity or slit lamp findings. There were also no significant between-group differences in the percent of subjects with a visual acuity change of two lines (0.2 logMAR units) or more.

Intraocular Pressure



There were no statistically significant differences between treatment groups in IOP at baseline or at the follow-up visit, and no significant difference between groups in changes from baseline in IOP. There was also no significant between-group differences in the percent of subjects with an IOP change of 6 mm Hg or more. During the study, two subjects in the 0.1% pemirolast group (Subjects 519 and 567) were noted with an increase from baseline of 6 mm Hg in both eyes and in one eye, respectively.

Dilated Fundus Examination

There were no differences between treatment groups for any of the ophthalmoscopic variables at baseline or the follow up visit. All subjects were noted with a normal (score of zero) retinal, macula, choroid, normal optic nerve, and normal vitreous in both eyes during the study.

8.1.1 Reviewer's Summary of Efficacy and Safety

Pemirolast demonstrates mild efficacy in the treatment/prevention of ocular itching and redness as demonstrated in statistically significant between-group differences in the primary efficacy variables.

Adverse experiences appeared mild to moderate in nature. The most serious events, repeated shoulder dislocation and severe anaphylactic reaction to baseline ragweed challenge, appear unrelated to treatment.

8 Clinical Studies

8.1.2 Study #2 Protocol 02-003

Title: A prospective, randomized, double-masked, parallel-group, multi-center comparison trial of the ocular efficacy and safety of 0.1% pemirolast potassium ophthalmic solution with that of placebo in subjects with a history of allergic conjunctivitis

Objective: The objective of this trial was to compare the efficacy and safety of 0.1% pemirolast potassium ophthalmic solution with placebo (vehicle) when administered bilaterally four times daily (QID) for approximately 9-16 weeks (depending on the length of the allergy season) in treating the ocular signs and symptoms associated with allergic conjunctivitis.

Study Design: A prospective, randomized, double-masked, parallel-group, multi-center study comparing 0.1% pemirolast with placebo (vehicle) in subjects with a history of allergic conjunctivitis. Study duration was 12-16 weeks at four study centers.

Test Drug Schedule: Subjects instilled 1-2 drops of either pemirolast 0.1% or vehicle four times a day (QID) in each eye beginning on Day 1 and continuing until 5-30 days after the first killing frost (Visit 5).

In addition, the investigator or his trained designee administered 1-2 drops of study medication in each of the subject's eyes 20 ± 1 minutes prior to allergen challenge at Visit 5.

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Gregg J. Berdy, MD (007) 456 North New Ballas Road Suite 386 Creve Coeur, MO 63141 (314) 993-5000	62	101-162	2 Aug 1997	13 Nov 1997	15 weeks

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Leonard M. Parver, MD (010) 456 North New Ballas Road Suite 386 Creve Coeur, MO 63141 (314) 993-5000	33	201-233	2 Aug 1997	20 Nov 1997	16 weeks
Jack V. Greiner, DO, PhD, OD (016) 7 Whittier Place, Suite 105 Boston, MA 02114 (617) 248-3875	23	163-170, 234-248	12 Aug 1997	5 Nov 1997	12 weeks
H. Jerome Crampton, MD (017) [redacted] 138 Haverhill Street Andover, MA 01810 (978) 475-0705	25	171-195	14 Aug 1997	3 Nov 1997	12 weeks

8.1.2 Study Design

This was a prospective, randomized, double-masked, parallel-group, multi-center study comparing 0.1% pemirolast with placebo (vehicle) in subjects with a history of allergic conjunctivitis. Approximately 120 subjects were planned to be enrolled in order to obtain 108 completed subjects (54 completed subjects per treatment group), assuming an estimated drop out rate of 10%. Visit 1 (Day 0, Baseline) occurred approximately 1-2 weeks prior to the average historical start date of the ragweed pollen season at each study center. Qualified subjects who met all required entry criteria, including a positive response to ragweed allergen challenge, were enrolled in the study, and randomly assigned to receive either 0.1% pemirolast or placebo. Subjects instilled 1-2 drops of masked study medication four times a day (QID) in each eye beginning on Day 1 and continuing until 5-30 days after the first killing frost (Visit 5). During the study, subjects recorded their ocular itching and redness in a diary each day at bedtime starting on Day 1 and continuing until 1-5 days after Visit 5 (Visit 6).

The study duration was to be approximately 9-16 weeks, depending on the length of the ragweed allergy season and occurrence of the first killing frost at each study center. Subjects returned for five scheduled follow-up visits: Day 7 ± 2 (Visit 2), Day 35 ± 3 (Visit 3), Day 56 ± 3 (Visit 4), 5-30 days after first killing frost (Visit 5), and 1-5 days

after Visit 5 (Visit 6). If applicable, subjects returned for a follow-up visit on Day 84 ± 3 (Interim Visit). In addition, subjects were contacted by telephone each week during those weeks that did not include a scheduled office visit.

Ophthalmic evaluations were performed at baseline and each scheduled follow-up visit, and included best-corrected visual acuity (ETDRS), slit-lamp examination (biomicroscopy), and ocular signs and symptoms. In addition, dilated fundus examinations (ophthalmoscopy) and IOP measurements were performed at Visits 1 and 6.

At Visit 5, subjects received 1-2 drops of study medication in each eye 20 ± 1 minutes prior to undergoing a second CAC with the same concentration of ragweed antigen that provoked a positive response at Visit 1. Post-challenge ocular signs and symptoms were recorded at 3, 10, and 20 minutes after challenge. Subjects were exited from the study at Visit 6.

Study Medications

Identical to Protocol 02-002, pg. 9, except that pemirolast Lot No. TC0636 was used.

Study Masking

This study used a double-masked design, in which the identities of the study medications were concealed from the subject and the investigator. During the study, no study medication was unmasked.

Reviewer's Comments:

Protocol 02-003 was not triple masked, as were Protocols 02-002 and 02-004. There were differences in the bottle configuration used for each of the two study medications. The identity of the study medications remained concealed from both subjects and investigators.

Study Population – Inclusion and Exclusion Criteria

Identical to Protocol 02-002 and Protocol 02-004, pg. 10.

Efficacy Variables

The primary efficacy variables in this study, as described in the protocol, included the following subject diary parameters:

- Worst Itching During the Day
- Bedtime Itching
- Bedtime Redness.

Subject diary variables were evaluated using 9-point scales (0-4 scale with half-grades allowed).

Secondary efficacy variables included the following pre-challenge and/or post-challenge ocular signs and symptoms. Variables were evaluated at each study visit using 9-point scales (0-4 scales with half-grades allowed).

- Ciliary Injection
- Episcleral Injection
- Conjunctival Injection

- Maximum Redness
  Maximum redness score was the greatest score among ciliary, episcleral, and conjunctival injection
- Chemosis
- Lid Swelling
- Tearing

- Itching
  Subjects evaluated ocular itching using the same 9-point scale as described above.
- Worst Itching During the First 10 Minutes after Challenge (evaluated only after allergen challenge at Visits 1 and 5) Subjects evaluated ocular itching using the same 9-point scale as described above.

Ocular signs and symptoms were evaluated at each study visit, and included the pre-challenge evaluations obtained at Visit 1 (Day 0, Baseline) and Visit 5 (5-30 days after the first killing frost), in addition to the evaluations obtained at follow-up visits without a CAC [Visit 2 (Day 7), Visit 3 (Day 35), Visit 4 (Day 56), Interim Visit (Day 84), and Visit 6 (1-5 days after Visit 5)].

Each day at bedtime during the study period, subjects recorded their exposure to the outdoors (outdoor exposure to Ragweed pollen) using a 3-point scale (0-2 scale).

Safety Variables

Identical to Protocol 02-002 and Protocol 02-004, pg. 14.

Table 10

Schedule of Visits and Measurements

Procedures	VISIT 1 Day 0, Baseline		VISIT 2	Telephone Contact 1	Telephone Contact 2	Telephone Contact 3	VISIT 3	Telephone Contact 4	Telephone Contact 5	VISIT 4
	Pre-CAC	Post-CAC	Day 7 ± 2	Day 14 ± 3	Day 21 ± 3	Day 28 ± 3	Day 35 ± 3	Day 42 ± 3	Day 49 ± 3	Day 56 ± 3
Informed Consent	X									
Medical History	X		X	X	X	X	X	X	X	X
Pregnancy Test	X									
Skin Prick Test	X									
Visual Acuity	X		X				X			X
Slit-Lamp Exam	X		X				X			X
Allergic Evaluation	X	X [1]	X				X			X
Investigator Instill Drug										
CAC (Ragweed)	X [2]									
Photographs										
Instill Relief Medication [3]		X								
IOP		X								
Fundus Exam (Dilated)		X								
Dispense Drug		X					X [4]			X [4]
Dispense Diary		X								
Diary Review/Record			X				X			X
Diary Review/Collect										
Collect Drug										
Exit Form										

[1] Post-CAC allergic evaluation performed 10 minutes after challenge.
[2] Determined allergen dose necessary to provoke ≥2+ ocular redness and itching OU.
[3] Approved topical ocular antihistamine/vasoconstrictor administered in each eye if necessary.
[4] Dispensed additional study medication if necessary.

Table 10
Schedule of Visits and Measurements (continued)

Procedures	Interim Telephone Contact [5] Day 63 ± 3	Interim Telephone Contact [5] Day 70 ± 3	Interim Telephone Contact [5] Day 77 ± 3	INTERIM VISIT [5] Day 84 ± 3	Interim Telephone Contact [5] Day 91 ± 3	Interim Telephone Contact [5] Day 98 ± 3	Interim Telephone Contact [5] Day 105 ± 3	VISIT 5 5-30 Days after First Killing Frost		VISIT 6 1-5 Days after Visit 5
								Pre-CAC	Post-CAC	
Informed Consent										
Medical History	X	X	X	X	X	X	X	X		X
Pregnancy Test										
Skin Prick Test										
Visual Acuity				X				X		X
Slit-Lamp Exam				X				X		X
Allergic Evaluation				X				X	X [6]	X
Investigator Instill Drug								X [7]		
CAC (Ragweed)								X [8]		
Photographs									X [9]	
Instill Relief Medication [10]									X	
IOP										X
Fundus Exam (Dilated)										X
Dispense Drug				X [11]						
Dispense Diary										
Diary Review/Record				X					X	
Diary Review/Collect										X
Collect Drug								X		
Exit Form										X

[5] Interim visit and interim telephone contacts occurred as scheduled until the first killing frost.
[6] Post-CAC allergic evaluations performed at 3, 10, and 20 minutes after challenge.
[7] Study medication administered 20 minutes prior to CAC.
[8] Used the allergen dose that provoked ≥2+ ocular redness and itching OU at Visit 1.
[9] Photographs of each eye were taken following the 10-minute post-challenge assessment.
[10] Approved topical ocular antihistamine/vasoconstrictor administered in each eye if necessary.
[11] Dispensed additional study medication if necessary.

Changes in the Planned Analyses

As planned in the protocol, subjects were enrolled at each study center approximately 1-2 weeks prior to the average historical start date of the ragweed allergy season. To adjust for differences among study centers in the actual start date of the ragweed pollen season, only subject diary data for those days occurring on or after the start date at each center were included in the study analyses. Diary data for days occurring before the start of the ragweed season were excluded from all efficacy analyses. At each center, the start of the ragweed season was defined as the first of two consecutive measurements of at least four (4) grains per cubic meter of ragweed pollen. The start dates of the ragweed allergy season at each study center appear below.

Investigator (ID No.)	First Subject Enrolled	Ragweed Season Start Date	Ragweed Pollen Count (Grains/m^3)
Gregg J. Berdy, MD (007)	2 August 1997	13 August 1997	12
Leonard M. Parver, MD (010)	2 August 1997	14 August 1997	4
Jack V. Greiner, DO, PhD, OD (016)	12 August 1997	16 August 1997	9
H. Jerome Crampton, MD (017)	14 August 1997	16 August 1997	9

Prevention of ocular signs or symptoms was included as a relevant study analysis, although it was not specified in the statistical analysis section of the protocol. Prevention of ocular itching or redness was assessed by calculating the daily percent of subjects with a score of zero in both eyes for each of worst itching during the day, bedtime itching, and bedtime redness.

Subject Disposition and Demographics

One hundred forty-three (143) subjects were enrolled in the study by four investigators, and 89% (127/143 subjects) completed the study as planned. The first subject was enrolled on August 2, 1997. The last subject exited on November 20, 1997.

Eleven percent (11%, 16/143) of the subjects were discontinued early, with 8% (6/71 subjects) in the 0.1% pemirolast group and 14% (10/72 subjects) in the placebo group. There was no statistically significant difference between treatment groups in the discontinuation rate. Reasons for discontinuation included: 10 subjects due to non-compliance (use of prohibited medications, missed visits, non-compliance with study medication regimen), four subjects due to improper entry, one subject due to lost to follow-up, and one subject due to an adverse event related to study medication (moderate ocular irritation).

Table 11
Subject Disposition

	Pemirolast N	Pemirolast %	Placebo N	Placebo %	Total N	Total %	P-Value
Enrolled	71	100.00	72	100.00	143	100.00	0.444
Completed	65	91.55	62	86.11	127	88.81	
Discontinued	6	8.45	10	13.89	16	11.19	
Non-Compliance	4	5.63	6	8.33	10	6.99	
Lost to Followup	1	1.41	0	0	1	0.70	
Adverse Event	0	0	1	1.39	1	0.70	
Improper Entry	1	1.41	3	4.17	4	2.80	

Table 12
Discontinued Subjects

Subject#	*Date*	*Exit Date*	*Reason*	*pemirolast 0.1%*
106	08/02/1997	09/27/1997	Non-Compliance	
116	08/02/1997	09/06/1997	Non-Compliance	
148	08/09/1997	08/09/1997	Improper Entry	
170	08/12/1997	09/03/1997	Lost to Follow-up	
186	08/14/1997	09/25/1997	Non-Compliance	
212	08/02/1997	11/15/1997	Non-Compliance	

Subject#	*Date*	*Exit Date*	*Reason*	*placebo*
105	08/02/1997	09/07/1997	Non-Compliance	
134	08/09/1997	09/04/1997	Non-Compliance	
142	08/09/1997	08/28/1997	Non-Compliance	
156	08/10/1997	08/10/1997	Improper Entry	
195	08/14/1997	08/15/1997	Improper Entry	
208	08/02/1997	08/02/1997	Improper Entry	
215	08/02/1997	09/06/1997	Non-Compliance	
221	08/02/1997	11/13/1997	Non-Compliance	
226	08/04/1997	09/08/1997	Non-Compliance	
242	08/12/1997	08/19/1997	Eye Irritation	

In the per-protocol group of subjects, there were no statistically significant differences between treatment groups in age, gender, race, or iris color. There were no statistically significant differences between treatment groups for any of the medical history variables.

Overall, there was no statistically significant difference between treatment groups in the mean concentration of ragweed antigen required to provoke a positive CAC response at Visit 1. However, when ragweed concentrations were examined by investigator, a significant between-group difference was observed at one study center. For Investigator 007, the mean concentration was approximately 3.7 times greater in the placebo group (342 AU/mL) than in the 0.1% pemirolast group (92 AU/mL) ($p=0.023$).

Table 13
Demographic Information – ITT Population

	Pemirolast	Placebo	Total	P-Value
Age				
N	70	69	139	0.994
Mean	34.97	34.96	34.96	
Std	10.00	11.90	10.95	
Min	10.00	14.00	10.00	
Max	57.00	66.00	66.00	

	Pemirolast		Placebo		Total		P-Value
	N	%	N	%	N	%	
Gender							0.548
Male	35	50.00	30	43.48	65	46.76	
Female	35	50.00	39	56.52	74	53.24	
Race							1.000*
Caucasian	57	81.43	56	81.16	113	81.29	
Black	12	17.14	10	14.49	22	15.83	
Hispanic	0	0	3	4.35	3	2.16	
Other	1	1.43	0	0	1	0.72	
Iris Color							0.271**
Dark Eyes	27	38.57	34	49.28	61	43.88	
Brown	27	38.57	33	47.83	60	43.17	
Black	0	0	1	1.45	1	0.72	
Light Eyes	43	61.43	35	50.72	78	56.12	
Blue	26	37.14	20	28.99	46	33.09	
Green	8	11.43	2	2.90	10	7.19	
	9	12.86	13	18.84	22	15.83	

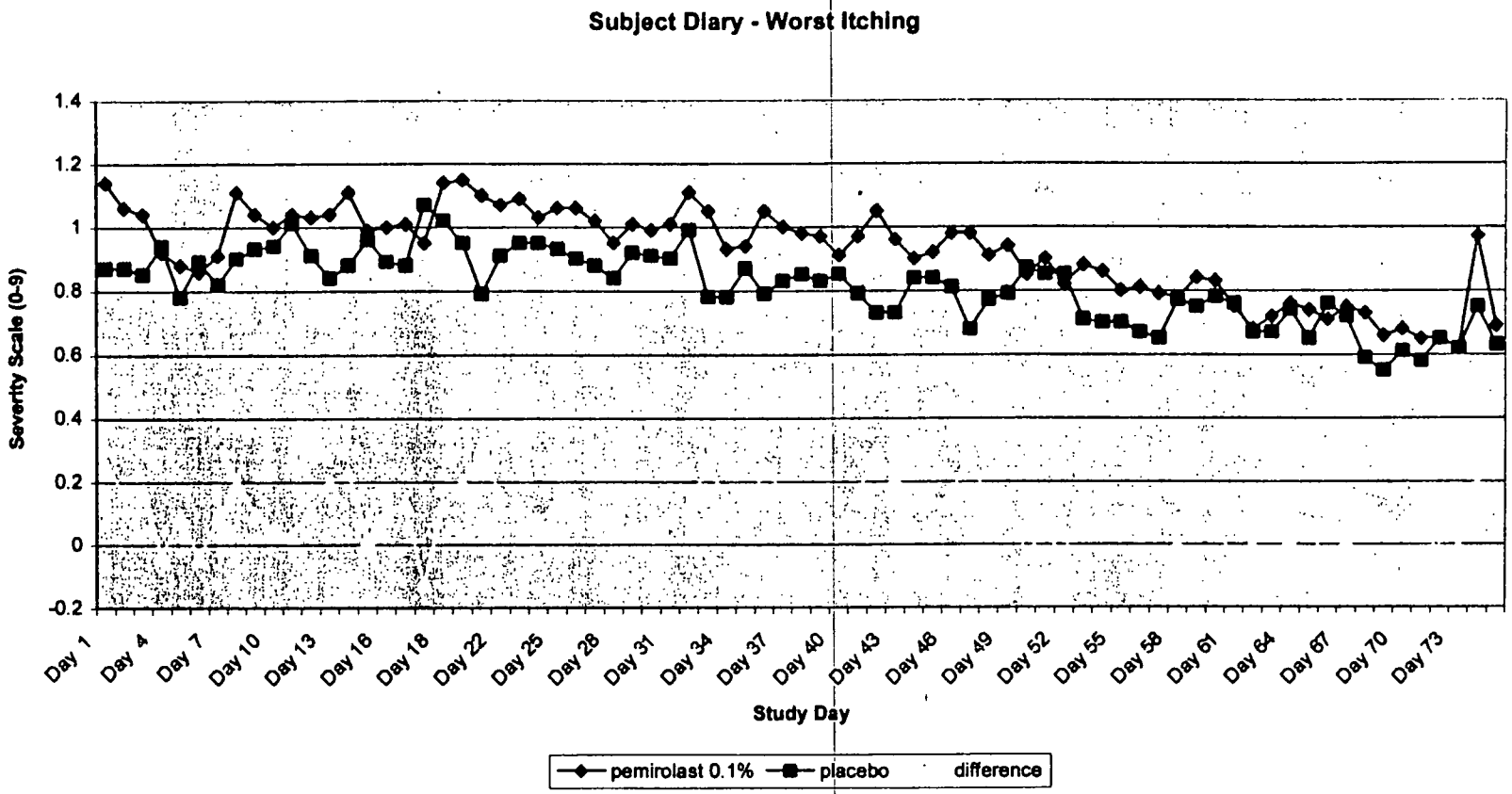
*Caucasian vs. Non-Caucasian
**Dark Eyes vs. Light Eyes

8.1.1 Efficacy – Protocol 02-003 Intent-to-Treat Population

Primary Efficacy Variables

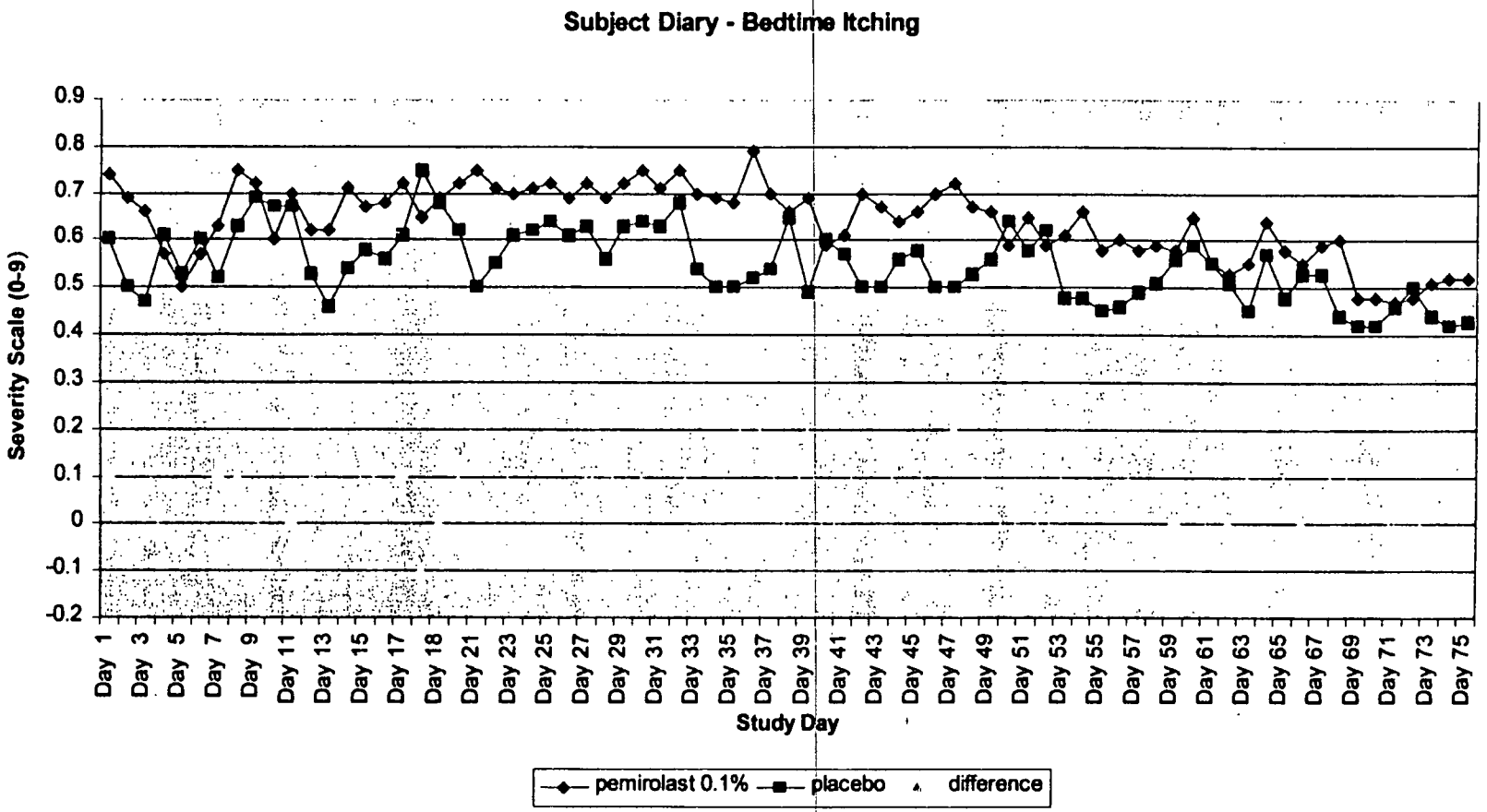
Reviewer's Comments:

Diary data evaluated to Day 75 – subject numbers precipitously dropped after that date.



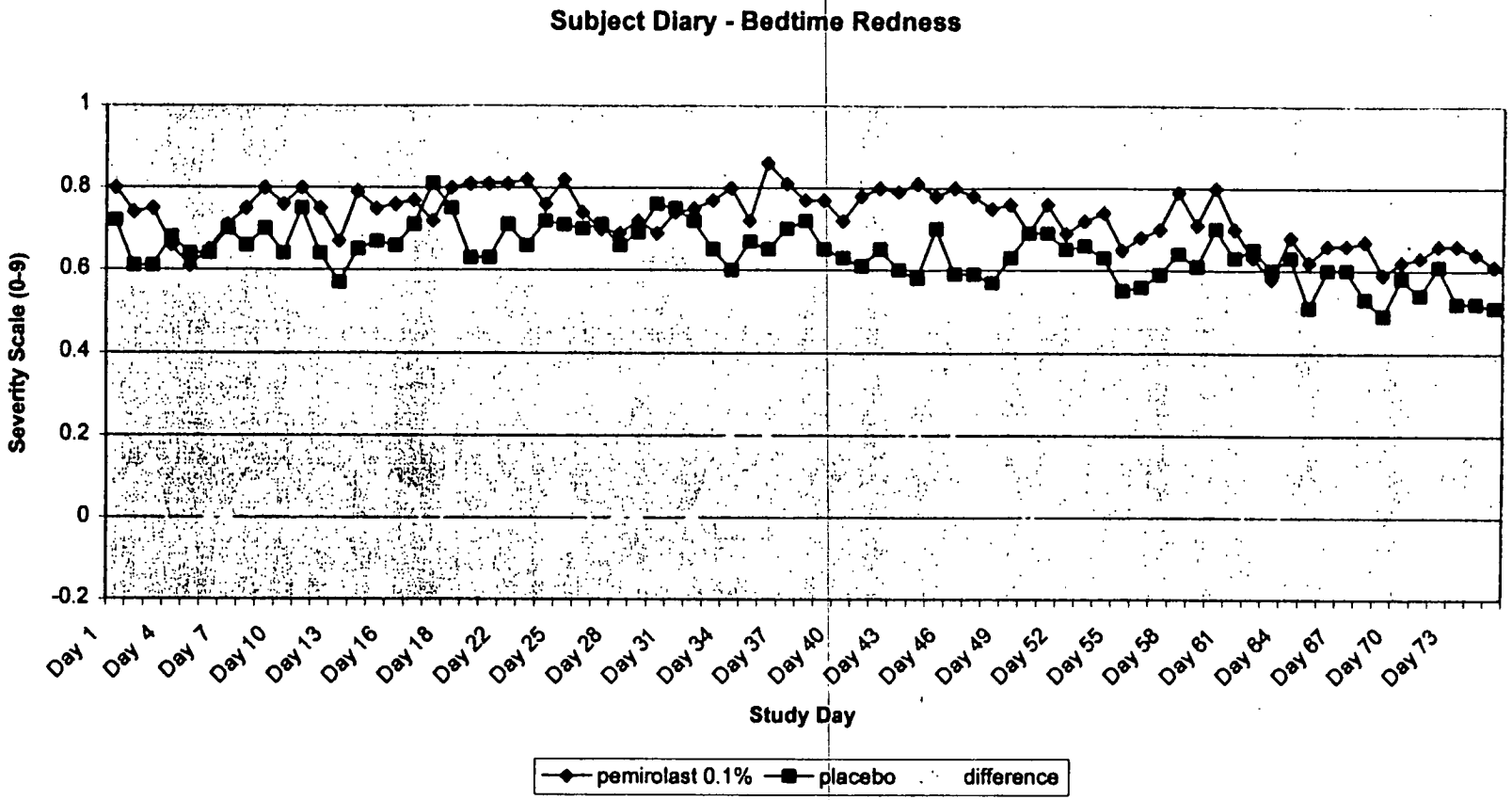
Subject Diary – Worst Itching

Worst itching during the day was lower in pemirolast-treated subjects than in placebo-treated subjects on only 7 out of 75 days. None of these between-group differences was statistically significant.



Subject Diary – Bedtime Itching

Bedtime itching during the day was lower in pemirolast-treated subjects than in placebo-treated subjects on only 8 out of 75 days. None of these between-group differences was statistically significant.



Subject Diary – Bedtime Redness

Ocular redness was lower in pemirolast-treated subjects than in placebo-treated subjects on only 1 out of 75 days. This between-group difference was not statistically significant.

Subject Diary – Worst Itching, Bedtime Itching, and Bedtime Redness: Percent of Subjects with a Score of Zero by Day

There were no statistically significant differences between treatment groups in the percent of subjects with no itching on any day during allergy season.

Although there were more reports of no redness in pemirolast-treated subjects than in vehicle-treated subjects, only one day out of 75 reached statistical significance.

Secondary Efficacy Variables

Secondary efficacy variables (ocular signs and symptoms): ciliary injection, episcleral injection, conjunctival injection, maximum redness (the greatest score among ciliary, episcleral, and conjunctival injection), chemosis, lid swelling, itching, and worst itching during the first 10 minutes after challenge.

Pre-Challenge Ocular Signs and Symptoms

There were no statistically significant differences between treatment groups for any of the ocular signs and symptoms at baseline (pre-challenge score at Visit 1) or any follow-up visit.

Post-Challenge Ocular Signs and Symptoms

Although statistically significant between-group differences were seen, the difference in mean scores for these variables was never more than 0.49 units.

Outdoor Exposure to Ragweed Pollen

There were no statistically significant differences between treatment groups in subject's recorded outdoor exposure to ragweed pollen during allergy season.

8.1.2 Safety

Adverse Events

Of the 139 subjects who used study medication, 106 subjects reported 299 adverse events during the study. There were no significant differences between treatment groups in overall adverse events or treatment-related events. The incidence of overall adverse events was 70% (49/70 subjects) in the 0.1% pemirolast group and 83% (57/69 subjects) in the placebo group. Most adverse events were of mild-to-moderate severity. There were no deaths, serious adverse events, or other significant events during the study.

There were no significant differences between treatment groups in the incidence of adverse events. The most frequently reported events were headache (47%, 66/139 subjects), rhinitis (33%, 46/139 subjects), and cold symptoms (14%, 19/139 subjects).

The incidence of ocular adverse events was 14% (20/139 subjects): 11% (8/70 subjects) in the 0.1% pemirolast group and 17% (12/69 subjects) in the placebo group. The most frequently reported ocular events were allergic conjunctivitis/allergy symptoms (4%, 5/139 subjects), dry eye (2%, 3/139 subjects), and conjunctival/limbal hyperemia eye (2%, 3/139 subjects).

Table 14
Adverse Events by Body System
Reported ≥ 3%

COSTART body system/ Preferred term	pemirolast 0.1%		vehicle	
	N	%	N	%
No Adverse Event	21	30.00	12	17.39
BODY/GEN				
Allerg React	2	2.86	4	5.80
Infec	8	11.43	11	15.94
BODY/HEAD				
Headache	31	44.29	35	50.72
RES/GEN				
Cough Inc	3	4.29	1	1.45
RES/NASP				
Pharyngitis	4	5.71	1	1.45
RES/NOSE				
Allerg React	1	1.43	3	4.35
Rhinitis	24	34.29	22	31.88
RES/SINUS				
Sinusitis	4	5.71	0	0
SS/EYE/CON				
Allerg React	1	1.43	4	5.80

Table 15
Serious Adverse Events

Investigator/Patient	Investigator's Adverse Event Description
pemirolast 0.1%	
10-231	Nasal congestion
16-244	Severe head cold
17-180	Excessive tearing - left eye
17-186	Headache
17-186	Sinus Congestion
placebo	
10-216	Migraine

Visual Acuity and Slit Lamp Exam

There were no statistically significant differences between treatment groups in best-corrected visual acuity or slit lamp exam at baseline or any follow-up visit, and no significant differences between groups in change from baseline in visual acuity or slit lamp exam.

Intraocular Pressure

There were no statistically significant differences between treatment groups in IOP at baseline or at the follow-up visit, and no significant difference between groups in changes from baseline in IOP. There was also no significant between-group differences in the percent of subjects with an IOP change of 6 mm Hg or more. During the study, 7 subjects were noted with an increase from baseline of 6 mm Hg or more: 5 subjects in the 0.1% pemirolast group (Subjects 132, 174, 187, 189, and 202) and 2 subjects in the placebo group (Subjects 193 and 234).

Dilated Fundus Examination

There were no differences between treatment groups for any of the ophthalmoscopic variables at baseline or the follow up visit.

8.1.2 Reviewer's Summary of Efficacy and Safety

Pemirolast does not demonstrate superiority over placebo in the treatment/prevention of ocular itching and redness. There are no statistically significant between-group differences in the primary efficacy variables. Adverse experiences are mild to moderate in nature.

One treatment center consistently favored placebo. At this center (Investigator 007), there was a significant between-group difference in baseline characteristics; patients assigned to receive 0.1% pemirolast required substantially lower ragweed exposure during the baseline allergen challenge in order to manifest approximately the same allergic response as patients assigned to receive placebo.

These results for this center suggested that between-group differences in ragweed sensitivity at this site might have interfered with the comparison of the two study treatments. Since this center enrolled a majority of patients, this difference between groups in reactivity to ragweed possibly confounded the overall efficacy results.

Protocol 02-003 also differs from Protocols 02-002 and-004 in two other ways. The drug lots of pemirolast 0.1% are different (-002 and –004 used the same lot numbers), and the trial was not "triple masked" because of a difference in the shape of the study bottles. Neither of these differences would be expected to account for the lack of efficacy in Protocol 02-003.

8 Clinical Studies

8.1.3 Study #3 Protocol 02-004

Title: A prospective, randomized, double-masked, parallel-group, multi-center comparison trial of the ocular efficacy and safety of 0.1% pemirolast potassium ophthalmic solution with that of placebo in subjects with a history of allergic conjunctivitis

Objective: The objective of this trial was to compare the efficacy and safety of 0.1% pemirolast potassium ophthalmic solution with placebo (vehicle) when administered bilaterally four times daily (QID) for approximately 9-16 weeks (depending on the length of the allergy season) in treating the ocular signs and symptoms associated with allergic conjunctivitis.

Study Design: A prospective, randomized, double-masked, parallel-group, multi-center study comparing 0.1% pemirolast with placebo (vehicle) in subjects with a history of allergic conjunctivitis. Study duration was 15-17 weeks at three study centers.

Test Drug Schedule: Subjects instilled 1-2 drops of either pemirolast 0.1% or vehicle four times a day (QID) in each eye beginning on Day 1 and continuing until 5-30 days after the first killing frost (Visit 5).

In addition, the investigator or his trained designee administered 1-2 drops of study medication in each of the subject's eyes 20 ± 1 minutes prior to allergen challenge at Visit 5.

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Thomas K. Mundorf, MD (011) [redacted] 1718 E. 4th Street, Suite 902 Charlotte, NC 28204 (704) 334-3222	62	301-348, 433-446	25 July 1997	24 Nov 1997	17 weeks

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Thomas John, MD (014) [redacted] 7060 Centennial Drive, Suite 103N Tinley Park, IL 60477 (708) 429-2223	21	401-421	27 July 1997	13 Nov 1997	16 weeks
John D. Lonsdale, MD (015) [redacted] 181 Russell Street Lewiston, ME 04240 (207) 784-1814	48	501-548	19 July 1997	3 Nov 1997	15 weeks

8.1.3 Study Design

Identical to Protocol 02-003, pg. 26.

Study Medications

Identical to Protocol 02-002, pg. 9.

Reviewer's Comments:

The same lots of pemirolast 0.1% and vehicle were used in Protocols 02-002 and 02-004. A different lot was used for the pemirolast 0.1% in Protocol 02-003.

Study Masking

Identical to Protocol 02-002, pg. 10.

Study Population – Inclusion and Exclusion Criteria

Identical to Protocol 02-002 and Protocol 02-003, pg. 10.

Efficacy Variables

Identical to Protocol 02-003, pg. 27.

Safety Variables

Identical to Protocol 02-002 and Protocol 02-003, pg. 14.

Schedule of Visits and Measurements

Identical to Protocol 02-003, pg. 29.

Changes in the Planned Analyses

Identical to Protocol 2-003, pg. 31.

The start dates of the ragweed allergy season at each study center appear below.

Investigator (ID No.)	First Subject Enrolled	Ragweed Season Start Date	Ragweed Pollen Count (Grains/m^3)
Thomas K. Mundorf, MD (011)	25 July 1997	4 August 1997	6
Thomas John, MD (014)	27 July 1997	15 August 1997	12
John D. Lonsdale, MD (015)	19 July 1997	16 August 1997	9

Subject Disposition and Demographics

One hundred thirty-one (131) subjects were enrolled in the study by three investigators, and 81% (106/131 subjects) completed the study as planned. The first subject was enrolled on July 19, 1997. The last subject exited the study on November 24, 1997.

Nineteen percent (19%, 25/131) of the subjects were discontinued early: 15% (10/67 subjects) in the 0.1% pemirolast group and 23% (15/64 subjects) in the placebo group. There was no statistically significant difference between treatment groups in the discontinuation rate. Reasons for discontinuation included: 12 subjects due to non-compliance (use of prohibited medications, missed visits, non-compliance with study medication regimen), three subjects due to lost to follow-up, three subjects due to personal decision, two subjects due to improper entry, and five subjects for other reasons (two subjects due to unresolved symptoms from Visit 1 allergen challenge, one subject due to relocation associated with a broken leg, one subject due to pregnancy, and one subject due to physician's decision).

Table 16
Subject Disposition

	Pemirolast N	Pemirolast %	Placebo N	Placebo %	Total N	Total %	P-Value
Enrolled	67	100.00	64	100.00	131	100.00	0.309
Completed	57	85.07	49	76.56	106	80.92	
Discontinued	10	14.93	15	23.44	25	19.08	
Non-Compliance	5	7.46	7	10.94	12	9.16	
Lost to Followup	2	2.99	1	1.56	3	2.99	
Subject Decision	1	1.49	2	3.13	3	2.29	
Improper Entry	0	0	2	3.13	1	1.53	
Other	2	2.99	3	4.69	5	3.82	

Table 17
Discontinued Subjects

Subject#	*Date*	*Exit Date*	*Reason*	*pemirolast 0.1%*
301	07/25/1997	09/24/1997	Relocation Asso'd with Broken Leg	
310	07/25/1997	11/03/1997	Non-Compliance	
313	07/25/1997	08/22/1997	Subject Decision	
338	07/31/1997	08/07/1997	Unresolved Sx from Visit 1 Challenge	
406	07/27/1997	08/03/1997	Lost to Follow-up	
413	07/27/1997	11/03/1997	Non-Compliance	
443	07/31/1997	09/26/1997	Non-Compliance	
502	07/19/1997	10/29/1997	Non-Compliance	
511	07/19/1997	09/26/1997	Non-Compliance	
525	07/19/1997	09/08/1997	Lost to Follow-up	

Subject#	*Date*	*Exit Date*	*Reason*	*placebo*
303	07/25/1997	09/19/1997	Improper Entry	
304	07/25/1997	10/14/1997	Non-Compliance	
317	07/25/1997	11/24/1997	Non-Compliance	
322	07/25/1997	09/11/1997	Unresolved Sx from Visit 1 Challenge	
328	07/31/1997	09/22/1997	Non-Compliance	
344	07/31/1997	11/14/1997	Non-Compliance	
347	07/31/1997	11/14/1997	Non-Compliance	
403	07/27/1997	08/08/1997	Non-Compliance	
411	07/27/1997	09/21/1997	Pregnancy	
433	07/31/1997	08/22/1997	Subject Decision	
506	07/19/1997	08/20/1997	Physician Decision	
522	07/19/1997	09/30/1997	Non-Compliance	
530	07/29/1997	09/12/1997	Improper Entry	
535	07/29/1997	08/04/1997	Subject Decision	
545	07/29/1997	08/12/1997	Lost to Follow-up	

In the intent-to-treat group of subjects, there were no statistically significant differences between treatment groups in age, gender, race or iris color.

There were no statistically significant differences between treatment groups for any of the medical history variables. There was also no significant between-group difference in the mean concentration of ragweed antigen needed to provoke a positive response to conjunctival allergen challenge at Visit 1.

Table 18
Demographic Information – ITT Population

	Pemirolast	Placebo	Total	P-Value
Age				
N	65	64	129	0.241
Mean	35.43	37.50	36.48	
Std	9.52	10.39	9.98	
Min	12.00	19.00	12.00	
Max	54.00	66.00	66.00	

	Pemirolast		Placebo		Total		P-Value
	N	%	N	%	N	%	
Gender							0.792
Male	34	52.31	31	48.44	65	50.39	
Female	31	47.69	33	51.56	64	49.61	
Race							0.057*
Caucasian	61	93.85	57	95.00	114	95.00	
Black	4	6.15	2	5.00	5	4.17	
Asian	0	0	1	1.56	1	0.78	
Hispanic	0	0	1	1.56	1	0.78	
Iris Color							0.061**
Dark Eyes	20	30.77	31	48.44	51	39.53	
Brown	18	27.69	29	45.31	47	36.43	
Black	2	3.08	2	3.13	4	3.10	
Light Eyes	45	69.23	33	51.56	78	60.47	
Blue	25	38.46	17	26.56	42	32.56	
Green	3	4.62	6	9.38	9	6.98	
Hazel	17	26.15	10	15.63	27	20.93	

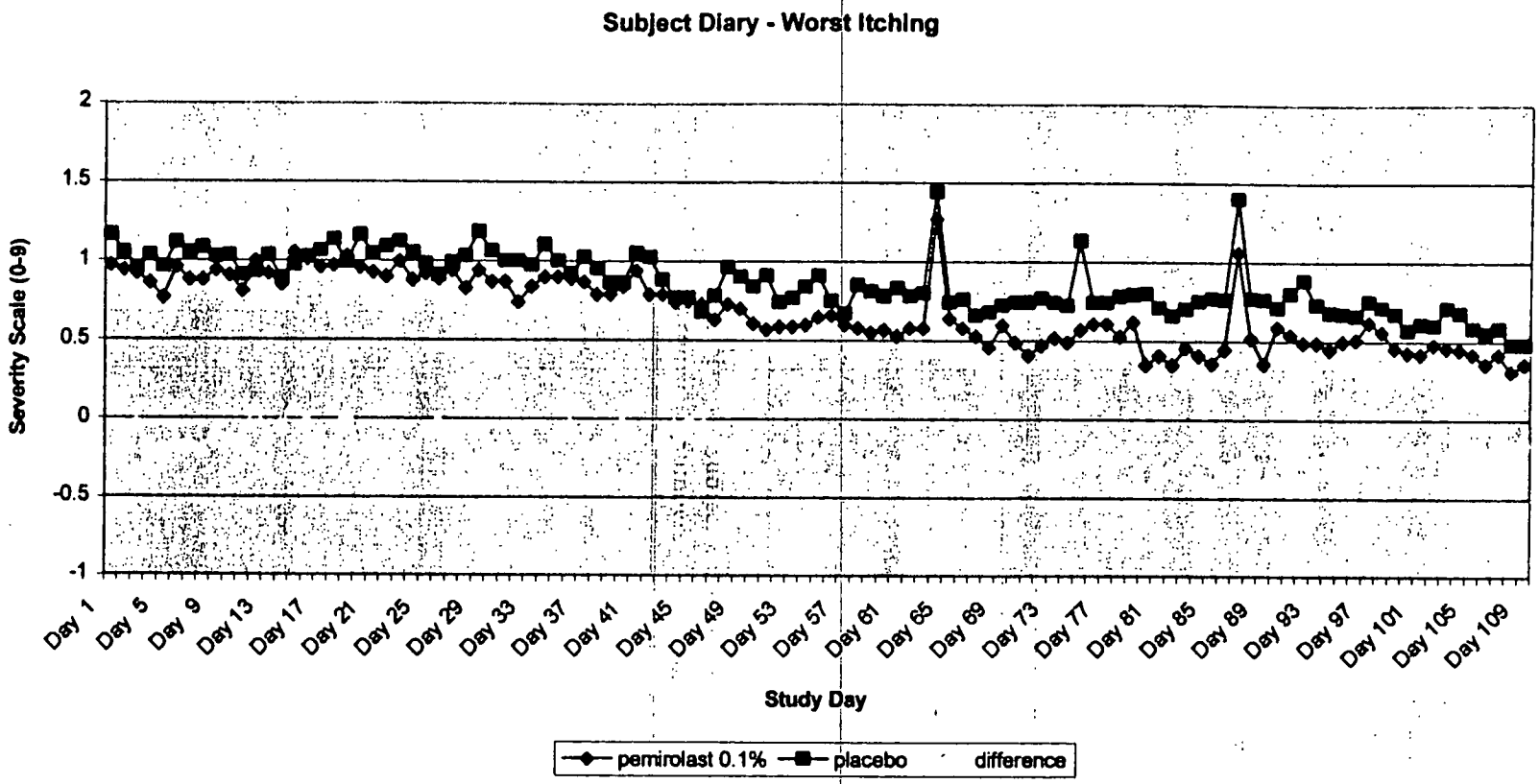
*Caucasian vs. Non-Caucasian
**Dark Eyes vs. Light Eyes

8.1.3 Efficacy – Protocol 02-004 Intent-to-Treat Population

Primary Efficacy Variables

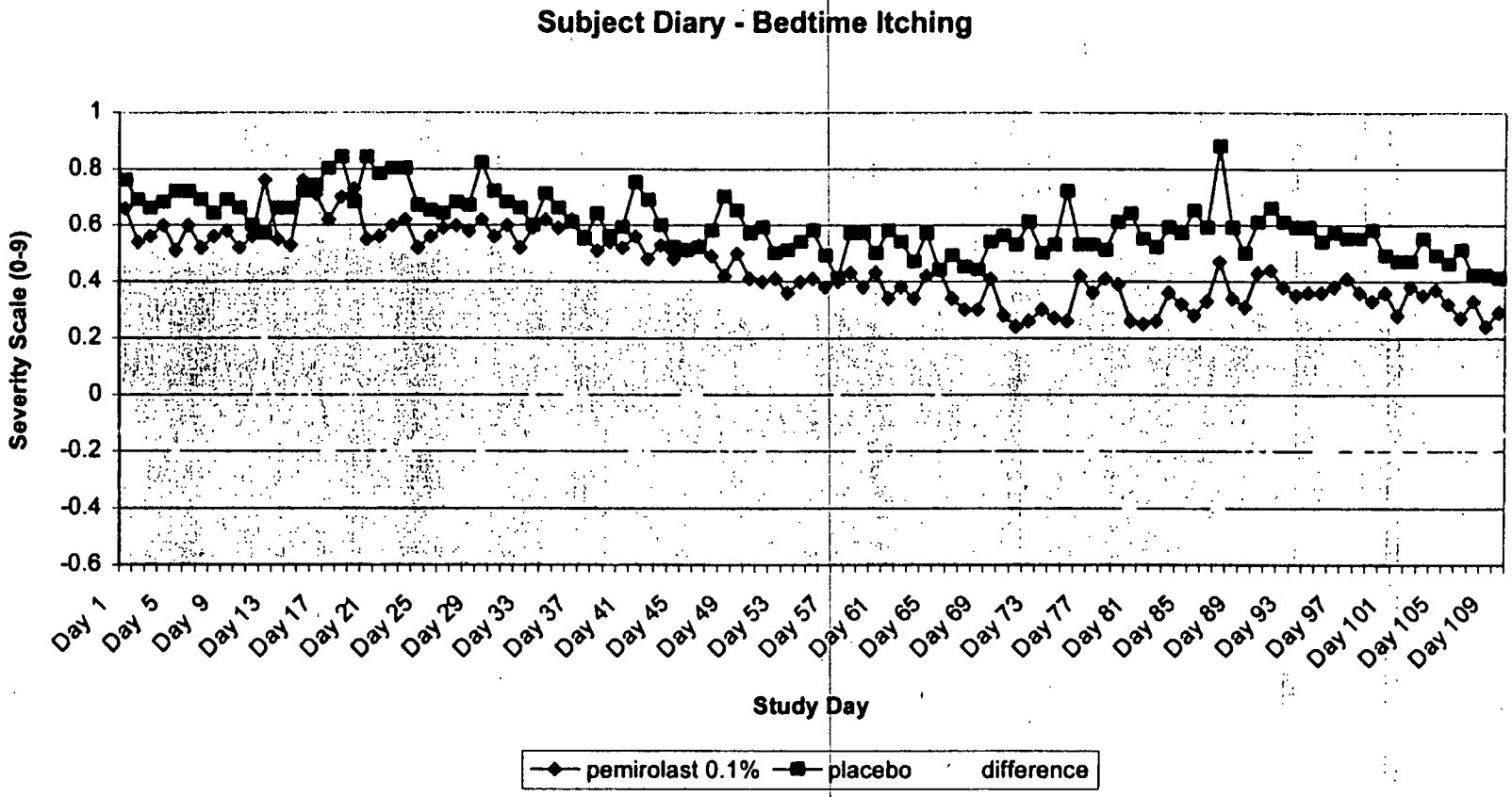
Reviewer's Comments:

Diary data evaluated to Day 109 – subject numbers precipitously dropped after that date



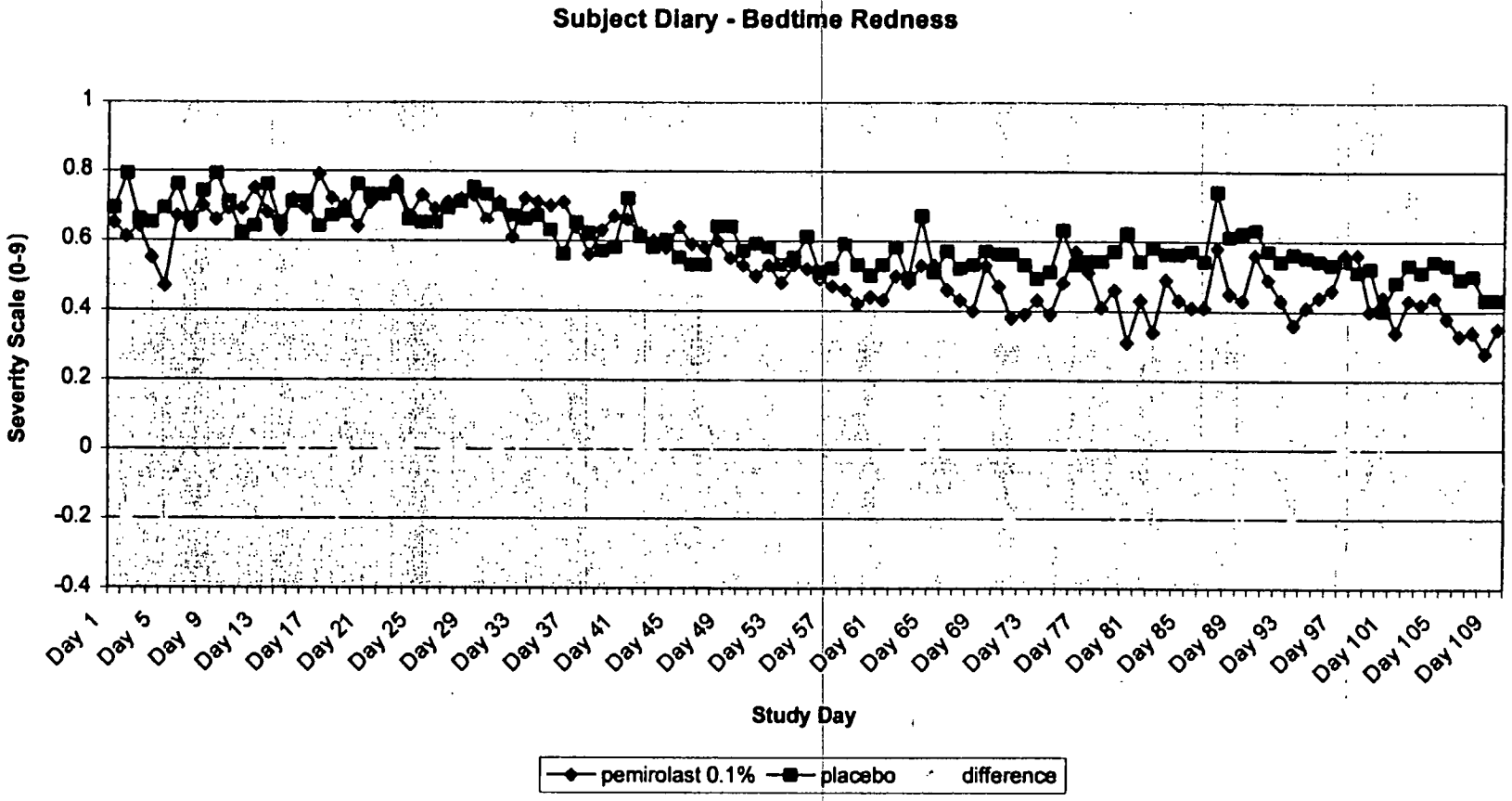
Subject Diary – Worst Itching

Worst itching during the day was lower in pemirolast-treated subjects than in placebo-treated subjects on 104 out of 109 days, with 46 days being statistically significant (primarily after Day 29). For 83% (90/109) of the days, the mean difference in itching was 0.10-0.45 units lower in the pemirolast 0.1% group than in the placebo group.



Subject Diary – Bedtime Itching

Ocular itching at bedtime was lower in pemirolast-treated subjects than in placebo-treated subjects on 104 out of 109 days, with 68 days being statistically significant (primarily after Day 21). For 72% (80/112) of the days, the mean difference in itching was 0.10-0.38 units lower in the pemirolast 0.1% group than in the placebo group.



Subject Diary – Bedtime Redness

Ocular redness at bedtime was lower in pemirolast-treated subjects than in placebo-treated subjects on 79 out of 109 days, with 32 days being statistically significant (primarily after Day 50). For 36% (39/109) of the days, the mean difference in itching was 0.10-0.31 units lower in the pemirolast 0.1% group than in the placebo group.

Subject Diary – Worst Itching, Bedtime Itching, and Bedtime Redness: Percent of Subjects with a Score of Zero by Day

Although there were more reports of no itching and no redness in pemirolast-treated subjects than in vehicle-treated subjects, only seven days showed statistical significance for Worst Itching, only four days for Bedtime Itching, and no days for Bedtime Redness.

Secondary Efficacy Variables

Identical to Protocol 02-003, pg. 28.

Pre-Challenge Ocular Signs and Symptoms

Although statistically significant between-group differences were seen, the difference in mean scores for these variables was never more than 0.14 to 0.19 units.

Post-Challenge Ocular Signs and Symptoms

Although one statistically significant between-group difference was seen, the difference in mean scores for this variable was never more than 0.46 units.

Outdoor Exposure to Ragweed Pollen

There were no statistically significant differences between treatment groups in subject's recorded outdoor exposure to ragweed pollen during allergy season.

8.1.3 Safety

Adverse Events

Of the 129 subjects who used study medication, 84 subjects reported 163 adverse events during the study. There were no significant differences between treatment groups in overall adverse events. The incidence of overall adverse events was 66% (43/65 subjects) in the 0.1% pemirolast group and 64% (41/64 subjects) in the placebo group. Most adverse events were of mild-to-moderate severity. There was one serious event, in which one subject in the 0.1% pemirolast group experienced a severe broken leg that was considered unrelated to use of the study medication. No deaths or other significant events occurred during the study.

There were no significant differences between treatment groups in the incidence of adverse events. The most frequently reported events were headache (18%, 23/129 subjects), rhinitis (14%, 18/129 subjects), and cold symptoms (10%, 13/129 subjects).

The incidence of ocular adverse events was 18% (23/129): 15% (10/65 subjects) in the 0.1% pemirolast group and 20% (13/64 subjects) in the placebo group. The most frequently reported ocular events were dry eye (5%, 6/129 subjects), burning/stinging

(3%, 4/129 subjects), eye pain (3%, 4/129 subjects), and foreign body sensation (3%, 4/129 subjects).

Table 19
Adverse Events by Body System
Reported ≥ 3%

COSTART body system/ Preferred term	pemirolast 0.1%		vehicle	
	N	%	N	%
No Adverse Event	22	33.85	23	35.94
BODY/GEN				
Allerg React	4	6.15	4	6.25
Flu Synd	2	3.08	0	0
Infect	11	16.92	2	3.13
BODY/HEAD				
Headache	13	20.00	10	15.53
DIG/BUC				
Tooth Dis	2	3.08	0	0
RES/GEN				
Dyspnea	1	1.54	2	3.13
RES/NASP				
Infect Bact	2	3.08	0	0
Pharyngitis	3	4.62	2	3.13
RES/NOSE				
Allerg React	6	9.23	3	4.69
Rhinitis	9	13.85	9	14.06
SKIN/GEN				
Pruritis	1	1.54	3	4.69
SS/EYE/GEN				
Burning Eye	3	4.62	1	1.56
Dry Eye	2	3.08	4	6.25
Foreign Body Sens	3	4.62	1	1.56
Pain Eye	2	3.08	2	3.13

Table 22
Serious Adverse Events

Investigator/Patient	Investigator's Adverse Event Description
pemirolast 0.1%	
11-301	Broken leg (right)
14-402	Cold symptoms, headache, cough, post-nasal drip
14-412	Headache
15-511	Cold with nasal congestion
15-518	Vertigo
placebo	
14-403	Burning eyes & nasal congestion following ragweed challenge 7/27/97
15-522	Upper respiratory infection

Visual Acuity and Slit Lamp Exam

There were no statistically significant differences between treatment groups in best-corrected visual acuity at baseline or any follow-up, and no significant differences between groups in change from baseline visual acuity.

There were no notable differences between treatment groups for any of the biomicroscopic variables at baseline or any follow-up visit. During the study, one subject experienced a change in biomicroscopy from normal to abnormal. For Subject 303 in the placebo group, a chalazion occurred in the OS lids at Visit 2 (Day 7), which was resolved by the following visit.

Intraocular Pressure

There were no statistically significant differences between treatment groups in IOP at baseline or at the follow-up visit, and no significant difference between groups in changes from baseline in IOP. There was also no significant between-group differences in the percent of subjects with an IOP change of 6 mm Hg or more.

During the study, one subject in the 0.1% pemirolast group (Subject 528) was noted with an increase from baseline of 7 mm Hg in one eye.

Dilated Fundus Examination

There were no statistically significant differences between treatment groups for any of the ophthalmoscopic variables at baseline or the follow up visit, and no subjects experienced an increase from baseline in any ophthalmoscopic variable. All subjects were noted with a normal (score of zero) optic nerve and vitreous in both eyes during the study.

8.1.3 Reviewer's Summary of Efficacy and Safety

Pemirolast demonstrates mild efficacy in the treatment/prevention of ocular itching (but not redness) as demonstrated in statistically significant between-group differences in the primary efficacy variables.

Adverse experiences appeared mild to moderate in nature. The most serious event, a broken leg, was unrelated to treatment (subject dove under a table during a robbery).

8 Clinical Studies

8.1.4 Study #4 Protocol 02-005

Title: A six-week, randomized, parallel group, single center comparison trial of the ocular safety of 0.1% pemirolast potassium ophthalmic solution with that of placebo in normal healthy children 3 to 5 years of age.

Objective: The objective of this trial was to compare the ocular safety of 0.1% pemirolast potassium ophthalmic solution to placebo (vehicle) when administered bilaterally four times daily (QID) for six weeks in healthy children three to five years of age with asymptomatic eyes.

Study Design: This was a 6-week randomized, parallel group, single center, placebo-controlled safety comparison of 0.1% pemirolast potassium ophthalmic solution to placebo (vehicle) in healthy children three to five years of age with asymptomatic eyes.

Test Drug Schedule: Subjects received either 0.1% pemirolast potassium ophthalmic solution or placebo (ratio 2:1) administered as one to two drops in both eyes QID for six weeks.

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Jay M. Rubin, M.D. (001) 999 E. Basse Rd, Suite 128B San Antonio, TX 78209	30	901-930	19 Oct 1997	30 Nov 1997	6 weeks

8.1.4 Study Design

This was a six-week randomized, parallel group, single center, placebo-controlled safety comparison of 0.1% pemirolast potassium ophthalmic solution to placebo used QID in healthy children three to five years of age with asymptomatic eyes. Enrolled subjects were randomly assigned to receive one to two drops of either 0.1% pemirolast potassium ophthalmic solution or placebo in both eyes QID for 6 weeks using a ratio of 2:1 (0.1% pemirolast potassium : placebo). At baseline (Visit 1, Day 1), Visit 2 (Day 7 ± 2), Visit 3 (Day 21 ± 3), and Visit 4 (Day 42 ± 3), subjects underwent visual acuity (HOTV test) and biomicroscopy examinations, and parents/guardians were queried regarding adverse events, compliance with dosing regimen, and medical and medication history. Between clinic visits, parents/guardians were contacted by telephone three times (Day

14 ± 2, Day 28 ± 3, and Day 35 ± 3) and again queried regarding adverse events, compliance, and medical/medication history.

Study Medications

Subjects received either 0.1% pemirolast potassium ophthalmic solution (Lot #TC0635) or pemirolast potassium vehicle (Lot #TC0638). Study medication was supplied in 10 cc bottles containing a 10 mL fill. The bottles were shipped to the clinical facilities labeled with the subject number, protocol number, and storage instructions.

Study Masking

Active (0.1% pemirolast potassium ophthalmic solution) and placebo (pemirolast potassium vehicle) study medication were identical in appearance. A scratch card concealing the description of the study medication was provided for each subject. In cases of a medical emergency, the investigator could reveal the treatment information by scratching the card, if it became necessary to know which study medication the subject received. During the study, no study medication was unmasked.

Study Population – Inclusion and Exclusion Criteria

30 healthy children three to five years of age with asymptomatic eyes were enrolled in the study. Only subjects meeting all eligibility requirements were enrolled into the study. All subjects' parents/guardians gave written informed consent for subjects prior to enrollment.

Inclusion Criteria

Subjects of either sex and any race meeting all of the following conditions were eligible for participation in this study:

- Subject and parent/guardian were willing to follow instructions and be able to make all the required study visits.
- Subject's parent/guardian was willing to give consent for subject.
- Subject was three to five years of age.
- Subject had to avoid disallowed medications during the study period.
- Subject had no abnormalities noted during the baseline ophthalmic examination that could interfere with the study parameters including, but not limited to, the safety evaluations of the study medication.

Exclusion Criteria

Subjects with any of the following conditions were not eligible for participation in this study:

- Presence of any significant illness that could be expected to interfere with the study.

- Regular use of topical ophthalmic solutions during the study, or less than one week before the study, including tear substitutes.
- Use of ophthalmic medications prior to the study which require longer than a one-week washout.
- Use of any systemic/topical investigational drug or device within 30 days before receipt of study medication.
- Ocular surgery within six months before the beginning of the study.
- History of allergy or hypersensitivity to any ophthalmic drug, including mast cell stabilizers or the preservative benzalkonium chloride (BAK).
- Presence of external ocular disease, inflammation or infection of the eye and/or eyelids including chronic or acute conjunctivitis.
- History of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome.
- Subjects with only one sighted eye or not correctable to 20/80 in both eyes.
- Stable immunotherapy for less than three months prior to initiation of the study.

Efficacy and Safety Variables

No efficacy data were collected in this study.

Safety was assessed by evaluating the incidence of adverse events, and changes from baseline in visual acuity and biomicroscopy measurements.

Table 21
Schedule of Visits and Measurements

	Visit 1 (Baseline)	Visit 2	Telephone Contact 1	Visit 3	Telephone Contact 2	Telephone Contact 3	Visit 4
Procedures	Day 1	Day 7± 2	Day 14± 2	Day 21± 3	Day 28± 3	Day 35± 3	Day 42± 3
Informed Consent	X						
Medical History	X	X	X	X	X	X	X
Visual Acuity	X	X		X			X
Biomicroscopy	X	X		X			X
Query for AEs		X	X	X	X	X	X
Dispense Drug	X	X *		X *			
Collect Drug							X
Exit Form							X

** If necessary*

APPEARS THIS WAY
ON ORIGINAL

Subject Disposition and Demographics

A total of 30 subjects were enrolled into the study and dosed with study medication: 20 subjects received 0.1% pemirolast potassium solution and 10 subjects received placebo. A total of 26 subjects completed the study: 17 in the 0.1% pemirolast potassium group and 9 in the placebo group. Three subjects were discontinued from the study after being lost to follow-up (two in the 0.1% pemirolast potassium group and one in the placebo treatment group) and one subject discontinued due to parent/guardian decision (0.1% pemirolast potassium group).

There were no significant differences between treatment groups regarding age, gender, or race. Of the 30 subjects enrolled in this study, 18 (60%) were Hispanic, 11 (36.67%) were Caucasian, and 1 (3.33%) was Black. Eleven (36.67%) subjects were female and 19 (63.33%) subjects were male. Subjects ranged in age from 3–5 years with a mean age of 4.00 (± 0.83) years. Eleven subjects were 3 years of age, 9 subjects were 4 years of age, and 10 subjects were 5 years of age. There were no significant differences between treatment groups regarding age, gender, or race.

Table 22
Discontinued Subjects

Subject No.	Treatment	AE's During Study	First Study Med Date	Last Drug Installation	Reason for Discontinuation
906	placebo	none	10/19/97	*	lost to follow-up
909	pemirolast 0.1%	none	10/19/97	*	lost to follow-up
910	pemirolast 0.1%	none	10/19/97	*	lost to follow-up
914	pemirolast 0.1%	none	10/19/97	10/21/97	subject or parent decision

*last drug date not available for subjects lost to follow-up

8.1.4 Efficacy

No efficacy data was collected in this study.

APPEARS THIS WAY
ON ORIGINAL

8.1.4 Safety Criteria

Adverse Events

Six of twenty (30%) subjects (Subject Nos. 901, 902, 915, 920, 921, and 924) in the 0.1% pemirolast potassium group and two of ten (20%) subjects (Subject Nos. 912 and 913) in the placebo group experienced a total of 12 and 2 adverse events (AEs), respectively, during the study period. The most common events were of the general body system including fever, flu syndrome, and accidental injury. The second most common events involved the eye, and included conjunctivitis, conjunctival discharge, discomfort (burning

sensation), foreign body in the cornea, papilledema, and hyperemia (secondary to being poked in the eye). Other events included diarrhea, cough, and urinary tract infection.

No AE was reported by more than one subject in either treatment group, and there were no statistically significant between-group differences observed in the incidence of AEs (p=0.682). See Tables 23 and 24.

Subject No. 912 in the placebo group experienced an adverse event considered severe in intensity. This subject lost consciousness for approximately 10 minutes secondary to a fall. The subject recovered without treatment.

There were no deaths or other significant adverse events during the study.

Reviewer's Comment's:

An adverse event experienced by subject #924 was coded as papilledema. Papilledema is listed throughout the sponsor's protocol summary as an adverse event.

In reviewing the data report listings, it became apparent that a "papillary reaction" at Visit 2 was miscoded as "papilledema." The sponsor was contacted to provide the Case Report Form for Visit 2. The Case Report Forms indicate the subject experienced a conjunctival papillary reaction rather than papilledema.

Visual Acuity

Reviewer's Comments:

There were no clinically significant differences between treatment groups in visual acuity at baseline or at any follow-up visit. See Graph pg. 58.

Biomicroscopy

The biomicroscopy evaluation assessing ocular signs and symptoms included examination of the lids, conjunctiva, cornea, anterior chamber, iris, lens, and vitreous. At baseline, most of the 30 subjects enrolled had normal biomicroscopy results for both the right (OD) and left (OS) eyes. In the 0.1% pemirolast potassium group (n = 20), abnormalities of the lids (nevus), conjunctiva (follicles), and cornea (scar) were noted in one (5%), five (25%), and one (5%) subject(s), respectively. In the placebo group (n = 10), abnormalities of the conjunctiva (follicles, cyst) and cornea (pannus) were noted in five (50%) and one (10%) subject(s), respectively.

Because of subject discontinuations, change values were available for only seventeen 0.1% pemirolast potassium and 9 placebo subjects. Changes from baseline (worsening) were noted for lids and/or conjunctiva in two subjects in the 0.1% pemirolast potassium group (Subject No. 921 [mattering of lids OU, bulbar injection OD, and papillary reaction of conjunctiva OU at Visit 4 only] and Subject No. 924 [mucous and papillary reaction of

the conjunctiva OS at Visit 2 only]). There were no changes from baseline (Visit 1, Day 1) of the cornea, anterior chamber, iris, lens, or vitreous for any subject at any visit.

Table 23
Summary of Adverse Events

	Treatment	
	pemirolast 0.1%	**placebo**
Number of Subjects	20	10
Number of Subjects with Adverse Events	6 (30.0%)	2 (20.0%)
Body/Gen	2 (10.0)	
Fever	1 (5.0)	
Flu Syndrome	1 (5.0)	1 (10.0)
Injury/Accident		1 (10.0)
Dig/Ec	1 (5.0)	
Diarrhea	1 (5.0)	
Res/Gen	1 (5.0)	
Cough Inc	1 (5.0)	
SS/Eye/Con	2 (10.0)	
Conjunctivitis	1 (5.0)	
Discharge Conjunc	1 (5.0)	
SS/Eye/Gen	2 (10.0)	
Discomfort	1 (5.0)	
Foreign Body Sensation	1 (5.0)	
Hyperemia	1 (5.0)	
SS/Eye/ON	1 (5.0)	
Papilledema	1 (5.0)	
UG/UT/Gen	1 (5.0)	
Urinary Tract Infection	1 (5.0)	

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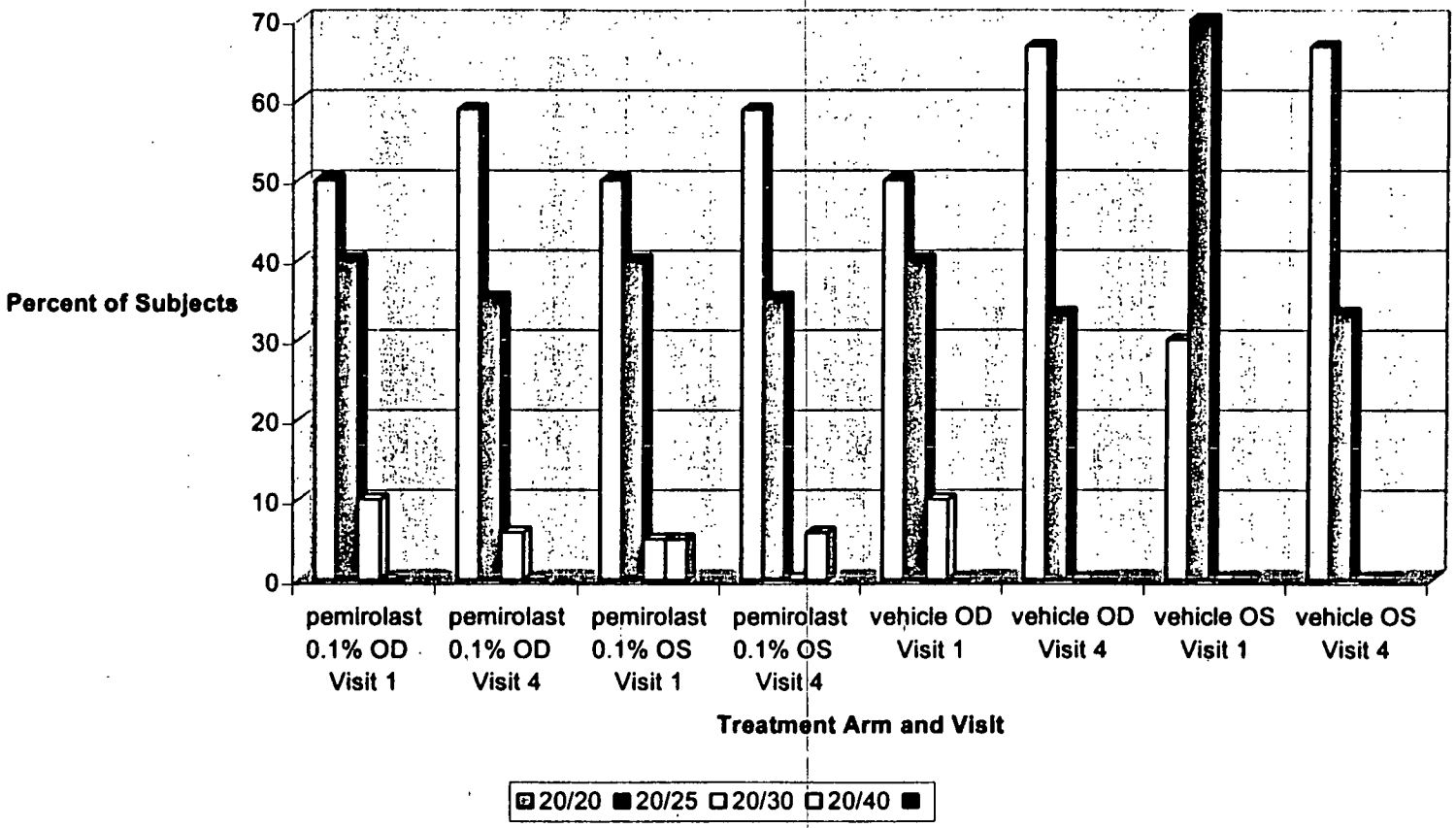
Table 24
Adverse Event Information

Subject #	Treatment	AE #	Adverse Event	Coded Term	Body System	Onset Date	Days After 1st Med	Severity	Outcome	Resolve Date
901	pemirolast 0.1%	1	redness OS – poked in eye with finger	hyperemia	SS/EYE/GEN	11/01/97	13	mild	resolved w/o tx	11/04/97
		2	corneal FB OS	foreign body sensation	SS/EYE/GEN	11/09/97	21	mild	resolved w/ tx	11/09/97
		3	cold	flu syndrome	BODY/GEN	11/08/97	20	mild	resolved w/ tx	11/24/97
902	pemirolast 0.1%	1	fever	fever	BODY/GEN	11/19/97	31	mild	resolved w/ tx	11/19/97
912	placebo	1	loss of consciousness due to fall	injury/accident	BODY/GEN	10/30/97	11	severe	resolved w/o tx	10/30/97
913	placebo	1	cold	flu syndrome	BODY/GEN	11/26/97	38	mild	resolved w/ tx	10/29/97
915	pemirolast 0.1%	1	diarrhea	diarrhea	DIG/EC	10/29/97	10	mild	resolved w/ tx	10/29/97
920	pemirolast 0.1%	1	burning sensation OD	discomfort OD	SS/EYE/GEN	11/09/97	21	mild	resolved w/o tx	11/09/97
921	pemirolast 0.1%	1	UTI	UTI	UG/UT/GEN	11/03/97	15	mild	resolved w/ tx	11/09/99
		2	conjunctivitis OU	conjunctivitis OU	SS/EYE/CON	11/30/97	42	mild	resolved w/ tx	12/05/97
924	pemirolast 0.1%	1	mucous OS	discharge conjunctiva	SS/EYE/CON	10/26/97	7	mild	resolved w/o tx	10/31/97
		2	papillary rxn OS	papilledema	SS/EYE/ON	10/26/97	7	mild	resolved w/o tx	11/11/97
		3	mucous OS	discharge conjunctiva	SS/EYE/CON	11/11/97	23	mild	resolved w/o tx	12/01/97
		4	cough	cough inc	RES/GEN	11/23/97	35	mild	resolved w/o tx	11/26/97

Visual Acuity - Visit 1 and Visit 4



8.1.4 Reviewer's Summary of Safety

No subjects discontinued the study prematurely due to adverse events. The 0.1% pemirolast ophthalmic solution when applied one to two drops in each eye QID for six weeks seemed well tolerated in children aged 3 to 5.

The sponsor is submitting an amendment to correct the miscoded conjunctival papillary reaction.

8 Clinical Studies

8.1.5 Study #5 Protocol 02-001

Title: Dose response of pemirolast potassium ophthalmic solution by provocative antigen challenge

Objective: The objective of this study was to compare the efficacy of two concentrations of pemirolast potassium ophthalmic solution versus placebo in the treatment of allergen-mediated conjunctivitis using a provocation challenge model and to determine the onset and duration of action of pemirolast potassium.

Study Design: A triple-masked, placebo-controlled, single center, randomized, two-arm, contralateral-eye comparison study in subjects with a history of allergic conjunctivitis. Study duration was approximately 5 weeks.

Test Drug Schedule: Subjects received either 0.1% pemirolast in one eye and placebo in the other eye or 0.25% pemirolast in one eye and placebo in the other eye. Subjects instilled 1-2 drops of study medication in the appropriate eye two times a day (BID) during the 7-day period prior to Visit 3 and during the 7-day period prior to Visit 4.

In addition, 1-2 drops of study medication were administered in the appropriate eye 10 minutes before allergen challenge at Visit 3, and four hours before allergen challenge at Visit 4.

Investigator (ID No.)	No. of Subjects Enrolled	Subject Numbers	First Subject Enrolled	Exit Visit for Last Subject	Study Duration
Mark B. Abelson, MD (003) [redacted] 863 Turnpike Street North Andover, MA 01845 (978) 685-8900	118	101-218	10 Mar 1996	2 May 1996	5 weeks

8.1.5 Study Design

This was a triple-masked, placebo-controlled, randomized, two-arm, contralateral-eye comparison study. Approximately 114 subjects were to be enrolled in order to obtain 102 completed subjects (51 subjects per treatment arm), based on a drop out rate of approximately 10%. Qualified subjects who elicited a positive allergen challenge response at Visit 1 (Screening Challenge) and Visit 2 (Confirmatory Challenge, ≥7 days after Visit 1) were enrolled into the study, and randomly assigned to receive one of the following treatment pairs: 0.1% pemirolast in one eye and placebo in the other eye, or 0.25% pemirolast in one eye and placebo in the other. Subjects instilled 1-2 drops of assigned study medication in the appropriate eye two times a day (BID) during the 7-day period prior to Visit 3 (Onset-of-Action Challenge, ≥14 days after Visit 2) and during the 7-day period prior to Visit 4 (Duration-of-Action Challenge, ≥14 days after Visit 3).

At Visit 3, 1-2 drops of assigned study medication were instilled in the appropriate eye 10 minutes prior to allergen challenge. Subjects were challenged with the final dose of antigen that elicited a positive response at Visit 1, and signs and symptoms of allergic conjunctivitis were assessed three (3 ± 1), ten (10 ± 1), and twenty (20 ± 1) minutes after challenge.

At Visit 4, 1-2 drops of assigned study medication were instilled in the appropriate eye four hours prior to allergen challenge. Subjects were challenged with the final dose of antigen that elicited a positive response at Visit 1, and signs and symptoms of allergic conjunctivitis were assessed three (3 ± 1), ten (10 ± 1), and twenty (20 ± 1) minutes after challenge.

Study Medications

Study medication was supplied in 10 cc bottles with a 10 ml fill, and were shipped to the investigator labeled with the subject number, the protocol number, and storage instructions. The following lots of study medication were used in this study:

Investigation Product	Concentration	Formulation No.	Lot No.
Pemirolast potassium ophthalmic solution	0.1%	1008S	6A9001
	0.25%	1009S	6B1001
Placebo (vehicle of pemirolast potassium)	0%	1007S	6B0001

Study Masking

This study used a triple-masked design, where the identity of the study medication was concealed from the subject, the investigator, and the Sponsor's monitors and clinical research personnel.

During the study, no study medication was unmasked in this fashion.

Study Population

To be enrolled in this study, subjects had to be at least 18 years old, have a history of seasonal allergic conjunctivitis or a positive diagnostic test, exhibit a positive reaction to antigen challenge in both eyes at Visit 1 (Screening Challenge) and Visit 2 (Confirmatory Challenge, ≥ 7 days after Visit 1), and have no evidence of signs and/or symptoms of allergic conjunctivitis at Visits 1 and 2.

Inclusion Criteria

Subjects were required to meet all of the following criteria to be eligible for participation in the study:

- History of seasonal allergic conjunctivitis or positive diagnostic test
- Positive reaction to antigen challenge in both eyes [≥2+ itching and ≥2+ redness in at least one of the three vessel beds (ciliary, episcleral, or conjunctival)] at Visit 1 (Screening Challenge) and Visit 2 (Confirmatory Challenge, ≥ 7 days after Visit 1)
- Ocular health within normal limits
- Must have been willing to avoid disallowed medication during the study
- Must have been willing to discontinue contact lens wear at least 72 hours before challenge and for the duration of the study
- Women of childbearing potential must have had a negative pregnancy test before entering the study and must use adequate birth control throughout the study period
- At least 18 years old
- Either sex or any race
- Must have been willing to follow instructions and be able to make all required study visits
- Must have been willing to give consent

Exclusion Criteria

Subjects with any of the following conditions were excluded from participating in the study:

- Females who were pregnant or were planning a pregnancy, did not utilize adequate birth control, or were not surgically sterile. A negative pregnancy test was required for women of childbearing potential.
- Presence of dry eye syndrome by history, blepharitis, follicular conjunctivitis, iritis or pre-auricular lymphadenopathy, or any other ophthalmic abnormality
- Contact lens wear up to less than 72 hours before challenge and during the study period
- Presence of bacterial or viral ocular infection, or positive history of ocular herpes
- Any systemic medication which may have interfered with the study: MAO inhibitors, non-steroidal anti-inflammatory agents (e.g., aspirin, ibuprofen), mast cell stabilizers, antihistamines, or steroids should have been discontinued 72 hours before the study and not used during the study
- Presence of any significant illness that could have been expected to interfere with the study, particularly any autoimmune disease such as rheumatoid arthritis, which can be associated with dry eye syndrome
- Regular use of topical ophthalmic solutions during the study, including tear substitutes; or use of any topical ophthalmic medication less than one week before the study. Subjects using ophthalmic medications that require longer than a one-week washout were not to be included in the study.
- Evidence of signs and/or symptoms of allergic conjunctivitis, i.e., greater than 1+ redness in any of the three vessel beds (ciliary, episcleral, conjunctival) and/or any itching at each baseline exam on Visits 1 or 2
- Use of any oral/topical investigational drug or device within 30 days before receipt of study medication
- Ocular surgery within 6 months before the beginning of the study
- History of uncontrolled cardiovascular, hepatic, and/or renal disease
- History of allergy or sensitivity to any mast cell stabilizer or to any ophthalmic drug, including the preservative(s)
- Current alcohol and/or drug abuse
- History of retinal detachment, diabetic retinopathy, or any retinal disease which may be progressive during the time course of the study
- Subjects with only one sighted eye or vision not correctable to 20/80 in both eyes
- Stable immunotherapy for less than 3 months prior to the initiation of the study

Additionally, the investigator or medical monitor could declare any subject ineligible for any sound medical reason.

Efficacy Variables

Primary Efficacy Variables

Primary efficacy variables included ocular (ciliary, episcleral, and conjunctival) injection, average redness (average of ciliary, episcleral, and conjunctival injection), and itching, which were assessed at 3, 10, and 20 minutes after allergen challenge at Visit 3 and Visit 4. Variables were graded using the following standardized 0-4 scales with half-grades allowed:

- Ocular Injection

  0.0 None. A normal, quiet eye; some subjects will exhibit rare vessels which are naturally prominent either by location or a large normal vessel diameter.

  1.0 Mild. Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantic.

  2.0 Moderate. More apparent dilation of blood vessels; vessel color is more intense (redder); involves the vast majority of the vessel bed.

  3.0 Severe. Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red - in the presence of chemosis, the leaking interstitial fluid may make the color appear less red or even pinkish; is not quadrantic.

  4.0 Extremely Severe. Large, numerous dilated blood vessels characterized by unusually severe deep red color, regardless of grade of chemosis, which involves the entire vessel bed.

- Average Redness

  The average redness score was the mean of ciliary, episcleral, and conjunctival injection scores.

- Itching

  0.0 None

  1.0 A tickling sensation, involving more than just the corner of the eye.

  2.0 A mild, continuous itch (can be localized) not requiring rubbing.

  3.0 A severe itch; which you would like to rub.

  4.0 An incapacitating itch which would require significant eye rubbing.

Secondary Efficacy Variables

Secondary efficacy variables included chemosis, lid swelling, and tearing, which were assessed at 3, 10, and 20 minutes after allergen challenge at Visit 3 and Visit 4. Variables were graded using a 0-4 scale with half-grades allowed (0.0 - None, 1.0 - Mild, 2.0 - Moderate, 3.0 - Severe, 4.0 - Extremely Severe).

Safety Variables

This study included the following safety variables:

- Adverse Events
  Subjects were queried at each follow-up visit regarding the occurrence of any adverse events.
- Best-Corrected Visual Acuity
  Best-corrected visual acuity was measured prior to allergen challenge at each study visit using a standard Snellen chart, and recorded in English units (e.g., 20/20).
- Slit-Lamp Examination Findings
  Biomicroscopy was performed prior to allergen challenge at each study visit. This examination included the lids, tear meniscus, conjunctiva, cornea, and lens. Variables were graded as normal or abnormal.

Table 25
Schedule of Visits and Measurements

Procedures	Screening Challenge [1]		Confirmatory Challenge [2]		Onset-of-Action Challenge		Duration-of-Action Challenge	
	VISIT 1		VISIT 2 ≥7 days after Visit 1		VISIT 3 ≥14 days after Visit 2		VISIT 4 ≥14 days after Visit 3	
	Pre-CAC	Post-CAC	Pre-CAC	Post-CAC 3, 10, 20 min	Pre-CAC	Post-CAC 3, 10, 20 min	Pre-CAC	Post-CAC 3, 10, 20 min
Informed Consent	X							
Medical History	X							
Pregnancy Test	X						X	
Diagnostic Skin Test (If necessary)	X							
Visual Acuity	X		X		X		X	
Ocular Signs and Symptoms	X	X	X	X	X	X	X	X
Slit-Lamp Exam	X		X		X		X	
CAC	X		X		X		X	
Fundus Exam (Undilated)	X							
Photographs				X [3]		X [3]		X [3]
Dispense Drug				X [4]		X [4]		
Drug Instilled by Investigator					10 min before CAC [5]		4 hrs before CAC [6]	
Exit Form								X

[1] Determined allergen dose required to elicit ≥2+ ocular redness and itching OU.
[2] Confirmed allergen dose required to elicit ≥2+ ocular redness and itching OU.
[3] Photographs of each eye were taken following the 10-minute post-challenge assessment.
[4] Instructed subjects to bilaterally instill appropriate study medication BID beginning seven (7) days prior to Visit 3 and Visit 4.
[5] Subjects were challenged 10 minutes after study medication instillation.
[6] Subjects were challenged 4 hours after study medication instillation.

Changes in the Planned Analyses

The following changes in the planned analyses were made due to the modest degree of effectiveness of pemirolast in both treatment groups:

- Demographic and baseline characteristics in each treatment group were tabulated using descriptive statistics only, and comparison of eye-specific baseline characteristics in pemirolast and placebo eyes were not performed.
- Comparisons of the efficacy of the two pemirolast concentrations (0.1% and 0.25%) were not performed.

In addition, a comparison of the number of adverse events in pemirolast-treated eyes vs. placebo-treated eyes was not performed due to the small number of ocular events that occurred during the study.

Subject Disposition and Demographics

One hundred eighteen (118) subjects were enrolled in this study: 60 subjects in the 0.1% pemirolast group and 58 subjects in the 0.25% pemirolast group. The first subject was enrolled on March 10, 1996. The last subject exited the study on May, 2, 1996.

Five percent (5%, 6/118) of the subjects were discontinued from the study early: 5% (3/60 subjects) in the 0.1% pemirolast group and 5% (3/58 subjects) in the 0.25% pemirolast group. Reasons for subject discontinuation included: two subjects due to health and safety in the 0.1% pemirolast group (Subject 114 due to conjunctivitis and Subject 211 due to pre-challenge redness and itching OS at Visit 4), two subjects due to lost to follow-up in the 0.25% pemirolast group (Subjects 190 and 200), one subject due to an adverse event in the 0.25% pemirolast group (Subject 173 due to corneal infiltrates OU), and one subject due to pregnancy in the 0.1% pemirolast group (Subject 149).

There were no notable differences between treatment groups in age, gender, race, or iris color. There were no notable differences between groups for any of the medical history variables.

8.1.5 Efficacy – Protocol 02-001 (No Excluded Data)

Primary Efficacy Variables

Pre-Challenge Ocular Injection and Itching

Reviewer's Comments:

There were no significant differences between treatment groups in pre-challenge ocular injection or itching at any visit.

Post-Challenge Ocular Injection and Itching

At Visits 1 and 2, there were no significant differences between treatment groups in post-challenge ocular injection and itching.

In the 0.1% pemirolast group, there were no clinically significant differences between pemirolast-treated eyes and placebo-treated eyes at Visit 3. Although statistically significant between-group differences were seen, the difference in mean scores for these variables was never more than 0.24 units.

In the 0.25% pemirolast group, there were no clinically significant differences between pemirolast-treated eyes and placebo-treated eyes.

Secondary Efficacy Variables

Pre- and Post-Challenge Ocular Signs and Symptoms

There were no significant differences between treatment groups in pre-challenge chemosis, lid swelling, or tearing at any visit.

In both the 0.1% and 0.25% pemirolast groups, there were no significant differences between pemirolast-treated eyes and placebo-treated eyes in mean scores for chemosis, lid swelling, and tearing at any post-challenge time point at any Visit.

8.1.5 Safety

Adverse Events

Table 26
Adverse Event Summary by Body System

Body System/Adverse Event	pemirolast 0.1%		pemirolast 0.25%	
	n	%	n	%
Body as a Whole				
flu syndrome	0	0	1	1.7
headache	8	13.3	5	8.6
infection	3	5.0	7	12.1
pain	1	1.7	0	0
pain back	1	1.7	0	0
Digestive				
abcess	0	0	1	1.7
pain	0	0	1	1.7
tooth caries	1	1.7	0	0
Respiratory				
bronchitis	0	0	1	0
cough inc	0	0	1	1.7
pharyngitis	1	1.7	0	0
rhinitis	0	0	2	3.4
Special Senses				
allergic Reac	1	1.7	0	0
infiltrate corneal	0	0	1	1.7

The incidence of any adverse event was 25% (15/60 subjects) in the 0.1% pemirolast group and 34% (20/58 subjects) in the 0.25% pemirolast group. The most frequently reported events were headache (11%, 13/118 subjects), cold symptoms (8%, 10/118 subjects), and rhinitis (2%, 2/118 subjects). Other non-ocular events included flu syndrome, back pain, knee pain, tooth abscess, tooth pain, dental caries, bronchitis, cough, and pharyngitis. All non-ocular adverse events were of mild-to-moderate severity.

There were no deaths or other significant events during this study.

Reviewer's Comments:

Adverse event table does not list a placebo column because all subjects received placebo.

Subject # 117 developed corneal infiltrates OU noted at Visit 3. Subject was discontinued from the study medication (0.25% pemirolast) and placed on PF QID. Infiltrates resolved within 6 days. Subject wore CL's but denied use during study.

Visual Acuity

There were no statistically or clinically significant differences between pemirolast-treated eyes and placebo-treated eyes or between the two treatment groups in visual acuity at any visit.

At Visit 3 and Visit 4, there were no notable differences between pemirolast-treated eyes and placebo-treated eyes or between the two treatment groups in changes from baseline (Visit 2) in visual acuity. At Visit 3, one eye treated with 0.1% pemirolast was noted with a two-line decrease from baseline. At Visit 4, two eyes treated with 0.1% pemirolast and two eyes treated with placebo (one eye in the 0.1% pemirolast group and one eye in the 0.25% pemirolast group) were noted with a two-line decrease from baseline.

Slit-Lamp Examination

There were no notable differences between pemirolast-treated eyes and placebo-treated eyes or between the two treatment groups in biomicroscopy findings at any visit. All biomicroscopy variables were normal at each visit, except for one subject in the 0.25% pemirolast group (Subject 173) who was noted with an abnormal cornea OU (corneal infiltrates OU) at Visit 3.

8.1.5 Reviewer's Summary of Efficacy and Safety

There are no clinically significant between-group differences in the primary efficacy variables.

One subject receiving 0.25% pemirolast was noted to have bilateral corneal infiltrates (thus one eye developed infiltrates while on vehicle treatment).

9 Overview of Efficacy

Marginal efficacy has been demonstrated in the treatment/prevention of ocular itching. This constitutes a marginal demonstration of the efficacy of pemirolast for the temporary relief of the itching due to seasonal allergic conjunctivitis when used QID.

10 Overview of Safety

Adequate safety has been established for use in the temporary relief of itching due to allergic conjunctivitis. Adequate safety has been established in children 3 to 5 years of age.

Adverse experiences appear mainly confined to mild to moderate events. The most frequent side effects are non-ocular, i.e. headache, rhinitis, and flu/cold symptoms. Ocular side effects were mild to moderate in severity in 2-3 % of subjects.

6 pages
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LABELING

12 Conclusions

The submitted studies in NDA 21-079 with the exception of Protocol 02-003 demonstrate safety and efficacy for the temporary prevention of itching of the eye due to seasonal allergic conjunctivitis.

13 Recommendations

1. *Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-079 is recommended for approval for the temporary prevention of itching of the eye due to seasonal allergic conjunctivitis.*

2. *The applicant should submit revised labeling consistent with the recommendations in this review.*

3. *Correction of a miscoded diagnosis in the Study Report of Protocol 02-005 should be made.*

/S/

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ON ORIGINAL

William M. Boyd
Medical Officer, Ophthalmology

NDA 21-079
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/ 5/3/99
HFD-550/Director/Midthun
HFD-880/Biopharm/Tandon
HFD-160/Micro/Hussong
HFD-550/Chem/Uppoor
HFD-550/PharmTox/Yang
HFD-715/Stat/Taneja
HFD-550/PM/Rodriguez, R
HFD-340/Carraras

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-079

NDA 21-079
Medical Officer's Review # 2

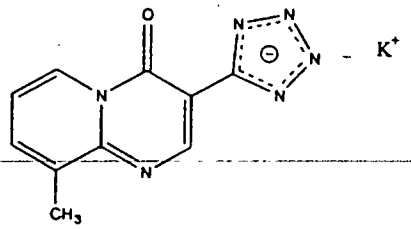
Submission: 8/11/99
Review Completed: 8/11/99

Proposed Tradename: Alamast

Generic Name: Pemirolast potassium ophthalmic solution, 0.1%

Chemical Name: 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-*a*]pyrimidin-4-one, potassium salt

4H-pyrido[1,2-a]pyrimidin-4-one,9-methyl-3-(1H-tetrazol-5-yl)-potassium



Chemical Structure – Formula $C_{10}H_7KN_6O$

Sponsor: Santen Incorporated
555 Gateway Drive
Napa, CA 94558

Pharmacologic Category: Mast cell stabilizer

Proposed Indication: ALAMAST™ ophthalmic solution is indicated for the prevention of itching of the eye due to allergic conjunctivitis. Symptomatic response to therapy (decreased itching) may be evident within a few days, but frequently requires longer treatment (up to four weeks).

Submitted: Revised labeling based on previous review and discussion with Pharm/Tox and the sponsor.

4 pages

REDACTED

DRAFT

LABELING

Recommendations:

NDA 21-079, Alamast (pemirolast potassium ophthalmic solution), 0.1% is recommended for approval for the prevention of itching of the eye due to allergic conjunctivitis. Symptomatic response to therapy (decreased itching) may be evident within a few days, but frequently requires longer treatment (up to four weeks).

A revised labeling review recommendation by Pharm/Tox to include the statement, "No adequate studies were conducted to assess the carcinogenic potential of pemirolast potassium," in the label was noted and overruled.

/S/

William M. Boyd
Medical Officer, Ophthalmology

Orig. NDA 21-079
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers
HFD-550/Director/Midthun
HFD-880/Biopharm/Tandon
HFD-160/Micro/Hussong
HFD-550/Chem/Uppoor
HFD-550/PharmTox/Yang
HFD-715/Stat/Taneja
HFD-550/PM/Rodriguez, R
HFD-340/Carraras

/S/ 8/19/99

Medical Officer's Review of NDA 21-079

NDA 21-079
Medical Officer's Review # 3

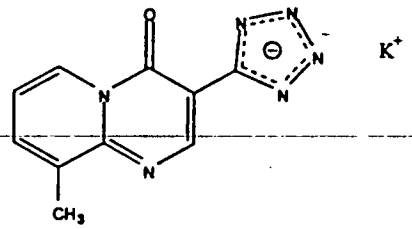
Submission: 9/23/99
Review Completed: 9/23/99

Proposed Tradename: Alamast

Generic Name: Pemirolast potassium ophthalmic solution, 0.1%

Chemical Name: 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-*a*]pyrimidin-4-one, potassium salt

4H-pyrido[1,2-a]pyrimidin-4-one,9-methyl-3-(1H-tetrazol-5-yl)-potassium



Chemical Structure – Formula $C_{10}H_7KN_6O$

Sponsor: Santen Incorporated
555 Gateway Drive
Napa, CA 94558

Pharmacologic Category: Mast cell stabilizer

Proposed Indication: ALAMAST™ ophthalmic solution is indicated for the prevention of itching of the eye due to allergic conjunctivitis. Symptomatic response to therapy (decreased itching) may be evident within a few days, but frequently requires longer treatment (up to four weeks).

Submitted: Revised labeling based on previous review and discussion with Pharm/Tox and the sponsor.

4 pages
REDACTED

DRAFT
LABELING

Recommendations:

NDA 21-079, Alamast (pemirolast potassium ophthalmic solution), 0.1% is recommended for approval for the prevention of itching of the eye due to allergic conjunctivitis. Symptomatic response to therapy (decreased itching) may be evident within a few days, but frequently requires longer treatment (up to four weeks).

After further discussion with the Pharm/Tox group, a sentence in the ***Carcinogenesis, mutagenesis, impairment of fertility*** *section of the label and a sentence in the Non-teratogenic effects section of the label have been revised for clarity.*

/S/

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ON ORIGINAL

William M. Boyd
Medical Officer, Ophthalmology

Orig. NDA 21-079
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/ 9/23/99
HFD-550/Director/Midthun
HFD-880/Biopharm/Tandon
HFD-160/Micro/Hussong
HFD-550/Chem/Uppoor
HFD-550/PharmTox/Yang
HFD-715/Stat/Taneja
HFD-550/PM/Rodriguez, R
HFD-340/Carraras

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-079
120-Day Safety Update

NDA 21-079
Medical Officer's Review

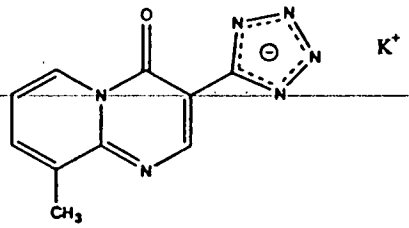
Submission: 7/23/99
Review Completed: 8/5/99

Proposed Tradename: Alamast

Generic Name: Pemirolast potassium ophthalmic solution, 0.1%

Chemical Name: 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-*a*]pyrimidin-4-one, potassium salt

4H-pyrido[1,2-a]pyrimidin-4-one,9-methyl-3-(1H-tetrazol-5-yl)-potassium



Chemical Structure – Formula $C_{10}H_7KN_6O$

Sponsor: Santen Incorporated
555 Gateway Drive
Napa, CA 94558

Pharmacologic Category: Mast cell stabilizer

Proposed Indication: Prevention and relief of ocular itching due to allergic conjunctivitis

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

Submitted:

A statement from Santen, Inc.:

There has been no new safety information learned about the drug that would reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

Reviewer's Comments and Conclusions:

Original conclusions regarding the safety of pemirolast potassium ophthalmic solution, 0.1% for the temporary prevention of itching of the eye due to allergic conjunctivitis are not altered.

/S/

APPEARS THIS WAY
ON ORIGINAL

William M. Boyd, M.D.
Medical Officer

NDA 21-079
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chamberl /S/ 8/4/99
HFD-550/Director/Midthun
HFD-880/Biopharm/Tandon
HFD-160/Micro/Hussong
HFD-550/Chem/Uppoor
HFD-550/PharmTox/Yang
HFD-715/Stat/Taneja
HFD-550/PM/Rodriguez, R
HFD-340/Carraras

APPEARS THIS WAY
ON ORIGINAL

Deputy Division Director's Review of NDA 21-079

NDA 21-079

Submission Dates: 3/25/99, 7/23/99, 8/4/99 & 8/5/99
Review Date: 8/6/99

Drug: Alamast (pemirolast potassium ophthalmic solution), 0.1%

Applicant: Santen Incorporated
555 Gateway Drive
Napa, CA 94558

Related Reviews:

Medical Officer's Review dated 7/19/99
Biopharm Review dated 7/14/99
Chemistry/Manufacturing Review dated 7/28/99
Pharmacology/Toxicology Review dated 7/30/99
Microbiology Review dated 6/18/99

I have reviewed the primary reviews for this application and concluded that the application should be recommended for approval pending revisions in the labeling described in the Medical Officer's Review and a commitment by the applicant to withdraw any lots of drug product which fall outside the stated specification. The applicant has submitted this commitment and revisions to the labeling in the submissions dated August 4 and 5, 1999.

Chemistry Manufacturing Review:

The Chemistry/Manufacturing Review identified a number of items listed as deficiencies. After review of these items, I have concluded that they are not items which are likely to affect the safety or efficacy of the proposed drug product for the following reasons:

[redacted]

Reviewer's Comments: *The applicant has identified the source of the starting materials in an amendment*

are commercially available.

4 pages

REDACTED

TRADE

secret/

Confidential

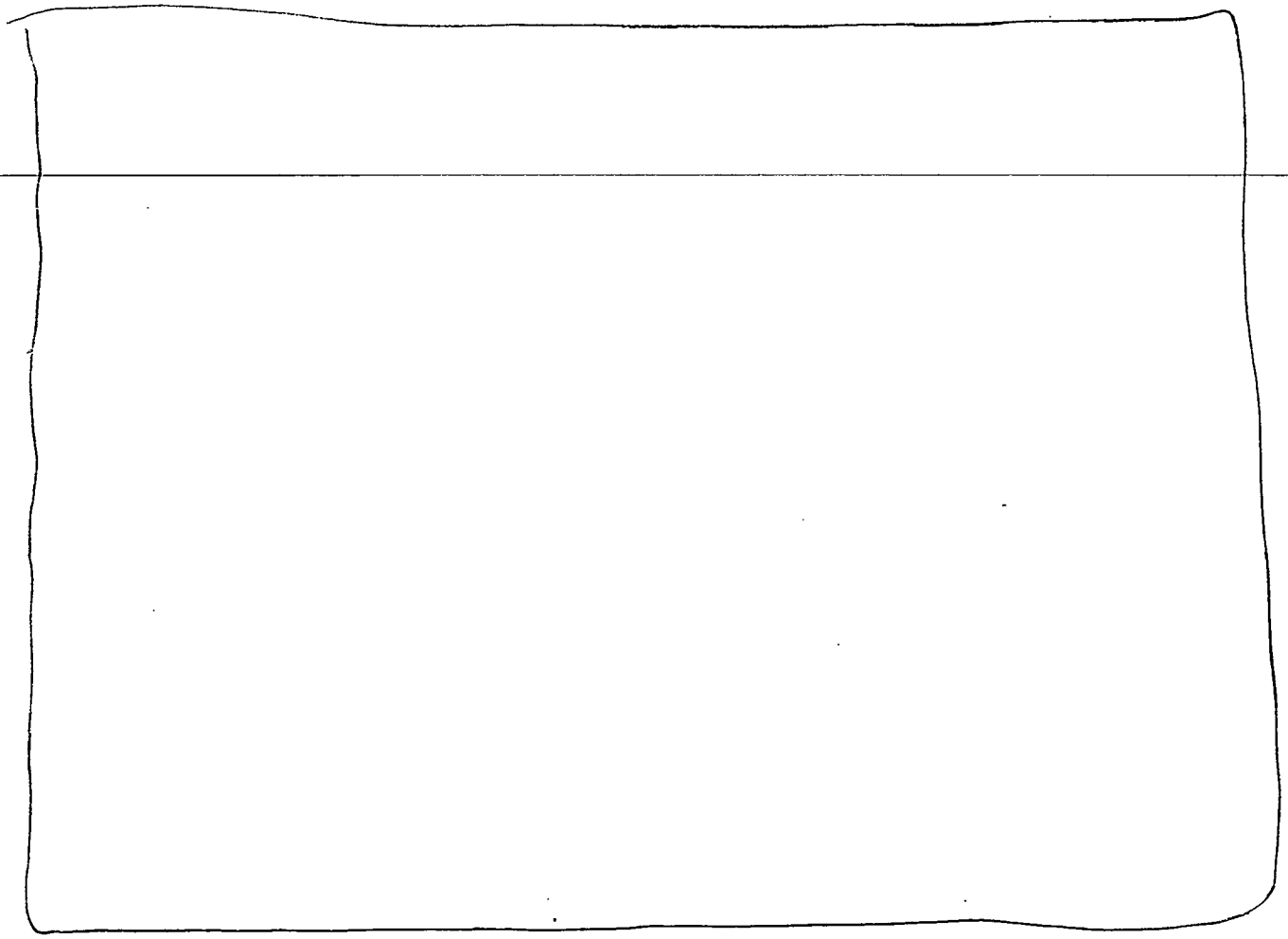
Commercial

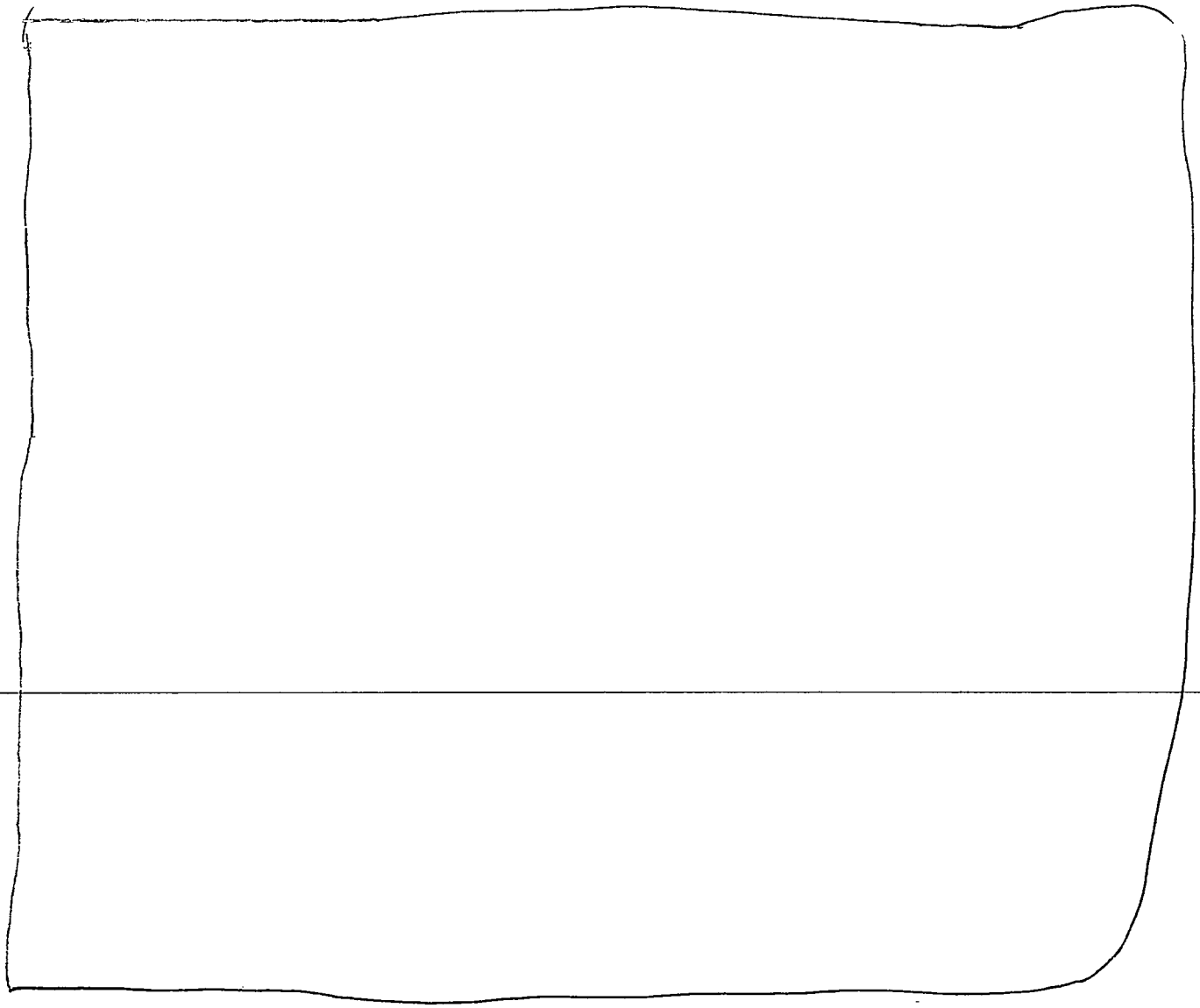
Clinical Pharmacology/Biopharmaceutics Review:

Reviewer's Comments: *Concur with the Overall conclusions, however, I disagree with several statements in the Background section of the review and some of the labeling recommendations. Specifically, corticosteroids are not "generally" used to treat allergic conjunctivitis and disodium chromoglycate is not approved for the treatment of allergic conjunctivitis. In addition, the half life and other specific pharmacokinetic parameters of oral dosing are not considered necessary for the understanding and proper administration of ophthalmic dosing of pemirolast.*

Microbiology Review/Sterility Issues:

The Microbiology Review identified a number of sterility assurance issues which have been address by the applicant in their amendment dated July 15, 1999. These issues are listed below and have satisfactorily addressed in the July 15, 1999 submission.





Recommendation:
NDA 21-079 is recommended for approval.

APPEARS THIS WAY
ON ORIGINAL

/S/

Wiley A. Chambers, M.D.

cc: NDA 21-079
HFD-550
HFD-550/MO/Boyd
HFD-550/PM/Rodriguez
HFD-830/CHEM/Uppoor
HFD-550/PHARM/Yang
HFD-550/Chambers

APPEARS THIS WAY
ON ORIGINAL

Deputy Division Director's Review of NDA 21-079

NDA 21-079	Submission Dates:	8/25/99 & 9/10/99 & 9/20/99
Review #2	Review Date:	9/21/99

Drug: Alamast (pemirolast potassium ophthalmic solution), 0.1%

Applicant: Santen Incorporated
555 Gateway Drive
Napa, CA 94558

Related Reviews:
Medical Officer's Review dated 7/19/99
Biopharm Review dated 7/14/99
Chemistry/Manufacturing Reviews dated 7/28/99 and 9/8/99
Pharmacology/Toxicology Review dated 7/30/99
Microbiology Review dated 6/18/99
Deputy Division Director's Review dated 8/6/99

Chemistry/Manufacturing review #3 is based on the applicant's response to Chemistry/Manufacturing review #1. The issues identified in that review were considered to be informational issues and not approvability issues in the Deputy Division Director's Review of 8/6/99. From a clinical prospective, these issues do not represent a safety concern.

Chemistry Manufacturing Review:

The Chemistry/Manufacturing Review identified a number of items listed as deficiencies. After review of these items, I have concluded that they are not items which are likely to affect the safety or efficacy of the proposed drug product for the following reasons:

Chemistry Post Approval Commitments

3 pages
REDACTED
TRADE Secret

Confidential
Commercial

Recommendation:
NDA 21-079 is recommended for approval.

/S/

Wiley A. Chambers, M.D.

cc: NDA 21-079
HFD-550
HFD-550/MO/Boyd
HFD-550/PM/Rodriguez
HFD-830/CHEM/Uppoor
HFD-550/PHARM/Yang
HFD-550/Chambers

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-079

REVIEW #: 1 **DATE OF REVIEW:** July 28, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	03/25/1999	03/26/1999	04/08/1999
Amendment, BC	06/25/1999	06/28/1999	07/09/1999

NAME & ADDRESS OF APPLICANT:

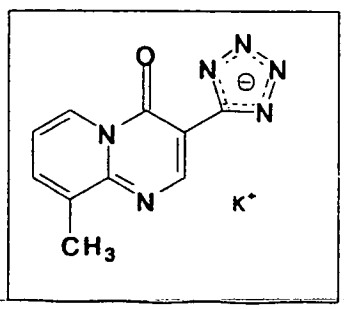
Santen Incorporated
555 Gateway Drive
Napa, CA 94558.
Contact: Michelle Carpenter, Director, Regulatory Affairs, 707-256-2453.
Form FDA 356h (7/97) signed by Merwin Jerry Hansen, CEO, Santen, Inc., 707-254-1750.

DRUG PRODUCT NAME
Proprietary: Alamast™.
Established: Pemirolast Potassium Ophthalmic Solution, 0.1%.
Code Name/#: TBX, BMY-26517, DE-068.
Chem.Type/Ther.Class: 1P.

PHARMACOL. CATEGORY: Mast Cell Stabilizer – Antiallergic.
DOSAGE FORM: Ophthalmic Solution.
STRENGTHS: 0.1% w/w.
ROUTE OF ADMINISTRATION: Topical ophthalmic drops.
PROPOSED USUAL DOSAGE: One or two drops in each affected eye four times daily.
DISPENSED: By prescription only. _X_ Rx __ OTC

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS REGISTRY #, AND STRUCTURAL FORMULA:

9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-α] pyrimidin-4-one, potassium salt, or
4H-pyrido[1,2-α] pyrimidin-4-one, 9-methyl-3-(1H-tetrazol-5-yl)-potassium.
$C_{10}H_7N_6KO$. MW=266.3. CAS Registry # 100299-08-9.



SUPPORTING DOCUMENTS:

IND#

DMF#	Type	Holder	Item/Component	Review Date	Status

CONCLUSIONS AND RECOMMENDATIONS:

In view of deficiencies identified in the CMC section of the application, from the CMC point of view, this application is recommended for an APPROVABLE action. Analytical methods validation is pending. The proposed trademark ALAMAST is acceptable. Based on stability data provided at this time, a shelf life of nine months is recommended for the drug product. Overall recommendation for the pre-approval inspections that have been requested is pending from the CDER Office of Compliance (please see EES print out dated 7/28/99, attached). Chemistry review related deficiencies identified on pages 69 and 70 of this review should be communicated to the applicant.

/S/ 07/28/99
Rajendra Uppoor, Ph.D., R.Ph.
Review Chemist, HFD-830/550

/S/ 7/30/99
Linda Ng, Ph.D.
Chemistry Team Leader, HFD-550

R. RODRIGUEZ

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-079

REVIEW #: 2 **DATE OF REVIEW:** August 20, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	03/25/1999	03/26/1999	04/08/1999
Amendment, BC	06/25/1999	06/28/1999	07/09/1999

The contents of the above two submissions were reviewed in Chemistry Review # 1, dated July 28, 1999. This review is for the following submissions, and for other issues that are mentioned in the review.

Amendment, BC	07/23/1999	07/26/1999	08/02/1999
Amendment, BZ	08/04/1999	08/06/1999	08/16/1999
Amendment, Fax	08/12/1999		

NAME & ADDRESS OF APPLICANT:

Santen Incorporated
555 Gateway Drive
Napa, CA 94558.
Contact: Michelle Carpenter, Director, Regulatory Affairs, 707-256-2453.
Form FDA 356h (7/97) signed by Merwin Jerry Hansen, CEO, Santen, Inc., 707-254-1750.

DRUG PRODUCT NAME
Proprietary: Alamast™.
Established: Pemirolast Potassium Ophthalmic Solution, 0.1%.
Code Name/#: TBX, BMY-26517, DE-068.
Chem.Type/Ther.Class: 1P.

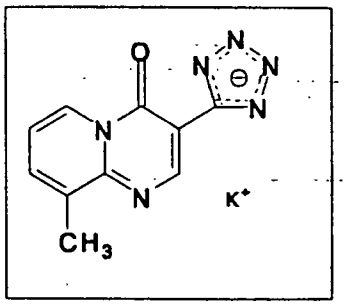
PHARMACOL. CATEGORY: Mast Cell Stabilizer – Antiallergic.
DOSAGE FORM: Ophthalmic Solution.
STRENGTHS: 0.1% w/w.
ROUTE OF ADMINISTRATION: Topical ophthalmic drops.
PROPOSED USUAL DOSAGE: One or two drops in each affected eye four times daily.
DISPENSED: By prescription only. _X_ Rx ___ OTC

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS REGISTRY #, AND STRUCTURAL FORMULA:

9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-α] pyrimidin-4-one, potassium salt, or
4H-pyrido[1,2-α] pyrimidin-4-one, 9-methyl-3-(1H-tetrazol-5-yl)-potassium.

NDA 21-079
Chemistry Review # 2

$C_{10}H_7N_6KO$. MW=266.3. CAS Registry # 100299-08-9.



CONCLUSIONS AND RECOMMENDATIONS:

In view of responses pending from the applicant for the chemistry deficiencies identified in the application, and communicated to the applicant through faxed lists of chemistry deficiencies, from the CMC point of view, this application continues to be recommended for an APPROVABLE action. Microbiology review of amendment dated 7/15/99 is pending. As of 8/20/99, overall recommendation for the pre-approval inspections that have been requested is pending from the CDER Office of Compliance (please see EES print out dated 8/20/99, attached). Analytical Methods validation is pending. Chemistry review related comments identified on page 13 of this review should be communicated to the applicant.

/S/ 08/20/99
Rajendra Uppoor, Ph.D., R.Ph.
Review Chemist, HFD-830/550

APPEARS THIS WAY
ON ORIGINAL

/S/ 8/20/99
Linda Ng, Ph.D.
Chemistry Team Leader, HFD-830/550

RELATED DOCUMENTS

Deputy Division Director's Review of NDA 21-079, dated 8/6/99.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA 21-079
HFD-550/Chemist/R.Uppoor
HFD-830/C-w.Chen
HFD-550/MO/W.Boyd
HFD-550/Division File
HFD-550/Chem.TL/L.Ng
HFD-550/CSO/R.Rodriguez
HFD-550/DDD/W.Chambers

Filename: C:\nda\21079rev2.

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-079

REVIEW #: 3 **DATE OF REVIEW:** September 8, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	03/25/1999	03/26/1999	04/08/1999
Amendment, BC	06/25/1999	06/28/1999	07/09/1999

The contents of the above two submissions were reviewed in Chemistry Review # 1, dated July 28, 1999.

Amendment, BC	07/23/1999	07/26/1999	08/02/1999
Amendment, BZ	08/04/1999	08/06/1999	08/16/1999
Amendment, NC	08/12/1999	08/16/1999	08/23/1999

The contents of the above three submissions were reviewed in Chemistry Review # 2, dated August 18, 1999.

The current Review # 3 evaluates the following:

Amendment, BC	08/25/1999	08/26/1999	09/03/1999

FDA CDER Office of Compliance, HFD-322, Memorandum dated 08/26/1999.

NAME & ADDRESS OF APPLICANT:

Santen Incorporated
555 Gateway Drive
Napa, CA 94558.
Contact: Michelle Carpenter, Director, Regulatory Affairs, 707-256-2453.
Form FDA 356h (7/97) signed by Merwin Jerry Hansen, CEO, Santen, Inc., 707-254-1750.

DRUG PRODUCT NAME
Proprietary: Alamast™.
Established: Pemirolast Potassium Ophthalmic Solution, 0.1%.
Code Name/#: TBX, BMY-26517, DE-068.
Chem.Type/Ther.Class: 1P.

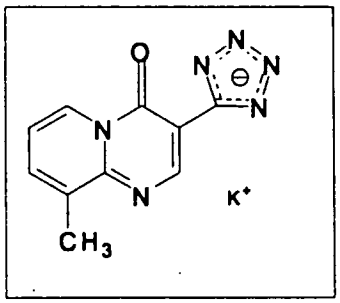
PHARMACOL. CATEGORY: Mast Cell Stabilizer – Antiallergic.
DOSAGE FORM: Ophthalmic Solution.
STRENGTHS: 0.1% w/w.
ROUTE OF ADMINISTRATION: Topical ophthalmic drops.
PROPOSED USUAL DOSAGE: One or two drops in each affected eye four times daily.
DISPENSED: By prescription only. _X_ **Rx** __ **OTC**

NDA 21-079
Chemistry Review # 3

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS REGISTRY #, AND STRUCTURAL FORMULA:

9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-α] pyrimidin-4-one, potassium salt, or
4H-pyrido[1,2-α] pyrimidin-4-one, 9-methyl-3-(1H-tetrazol-5-yl)-potassium.

$C_{10}H_7N_6KO$. MW=266.3. CAS Registry # 100299-08-9.



APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS AND RECOMMENDATIONS:

From the CMC point of view, this application is recommended for an APPROVAL action contingent upon completion of a satisfactory microbiology review and resolution of issues identified on page 15 of this review. Based on data provided in the application and its amendments, a shelf-life of 18 months is recommended for the drug product. Microbiology review of amendment dated 7/15/99 is pending. Analytical Methods Validation is pending. Chemistry review related comments identified on page 15 of this review should be communicated to the applicant.

/S/ 09/08/99
Rajendra Uppoor, Ph.D., R.Ph.
Review Chemist, HFD-830/550

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/8/99
Linda Ng, Ph.D.
Chemistry Team Leader, HFD-830/550

Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-079

CHEMIST'S REVIEW #: 4 **DATE OF REVIEW:** September 21, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	03/25/1999	03/26/1999	04/08/1999
Amendment, BC	06/25/1999	06/28/1999	07/09/1999

The contents of the above two submissions were reviewed in Chemistry Review # 1, dated July 28, 1999.

Amendment, BC	07/23/1999	07/26/1999	08/02/1999
Amendment, BZ	08/04/1999	08/06/1999	08/16/1999
Amendment, NC	08/12/1999	08/16/1999	08/23/1999

The contents of the above three submissions were reviewed in Chemistry Review # 2, dated August 18, 1999.

Chemist's Review # 3 dated September 8, 1999 evaluated the following:

Amendment, BC	08/25/1999	08/26/1999	09/03/1999

FDA CDER Office of Compliance, HFD-322, Memorandum dated 08/26/1999.

The current Chemist's Review # 4 evaluates the following:

Amendment	09/20/1999

NAME & ADDRESS OF APPLICANT:

Santen Incorporated
555 Gateway Drive
Napa, CA 94558.
Contact: Michelle Carpenter, Director, Regulatory Affairs, 707-256-2453.
Form FDA 356h (7/97) signed by Merwin Jerry Hansen, CEO, Santen, Inc., 707-254-1750.

DRUG PRODUCT NAME
Proprietary: Alamast™.
Established: Pemirolast Potassium Ophthalmic Solution, 0.1%.
Code Name/#: TBX, BMY-26517, DE-068.
Chem.Type/Ther.Class: 1P.

PHARMACOL. CATEGORY: Mast Cell Stabilizer – Antiallergic.
DOSAGE FORM: Ophthalmic Solution.
STRENGTHS: 0.1% w/w.
ROUTE OF ADMINISTRATION: Topical ophthalmic drops.
PROPOSED USUAL DOSAGE: One or two drops in each affected eye four times daily.

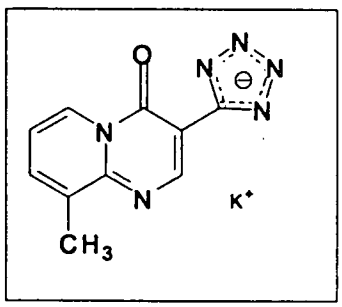
NDA 21-079
Chemistry Review # 4

DISPENSED: By prescription only. X Rx __ OTC

CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, CAS REGISTRY #, AND STRUCTURAL FORMULA:

9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-α] pyrimidin-4-one, potassium salt, or
4H-pyrido[1,2-α] pyrimidin-4-one, 9-methyl-3-(1H-tetrazol-5-yl)-potassium.

$C_{10}H_7N_6KO$. MW=266.3. CAS Registry # 100299-08-9.



APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS AND RECOMMENDATIONS:

From the CMC point of view, this application is recommended for an APPROVAL action contingent upon completion of satisfactory microbiology review. Analytical methods validation is pending. A paragraph should be added in agency's action letter regarding continued cooperation from the applicant to resolve issues that may be identified during methods validation at FDA laboratories. Reference to Santen's commitments submitted to the application (in their amendment dated 9/20/99) to perform drug substance and drug product testing should also be included in agency's letter.

/S/ 09/21/99
Rajendra Uppoor, Ph.D., R.Ph.
Review Chemist, HFD-830/550

APPEARS THIS WAY
ON ORIGINAL

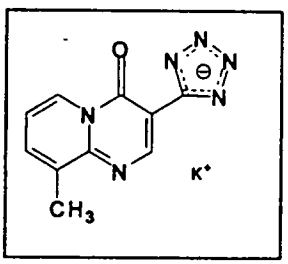
/S/ 9/21/99
Linda Ng, Ph.D.
Chemistry Team Leader, HFD-830/550

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA	**21-079**
DRUG:	Alamast™ [Pemirolast Potassium Ophthalmic Solution, 0.1%]
CODE NAMES:	TBX, BMY-26517, DE-068, BLX
SPONSOR:	Santen Incorporated, 555 Gateway Drive, Napa, CA 94558
SUBMISSION DATE:	March 25, 1999
TYPE OF SUBMISSION:	Original, 505 (b) (1)
DATE COMPLETED:	July 30, 1999
REVIEWER:	W. C. Josie Yang, DVM, Ph.D.
INFORMATION TO SPONSOR:	**Yes**
CDER STAMP DATE:	March 26, 1999
DATE RECEIVED IN HFD-550:	March 29, 1999
DATE ASSIGNED TO REVIEWER:	April 1, 1999
USER FEE DUE DATE:	September 26, 1999
DRUG CATEGORY:	Anti-allergic Agent (Mast Cell Stabilizer)
FORMULA:	$C_{10}H_7N_6KO$; 1-methyl-3-(1H-tetrazol-5yl)-4H-pyrido[1,2-a] pyrimidin-4-one-potassium; MW=266.3

Ingredient	Quantity(mg/ml)	Percent (w/v)
Pemirolast potassium		
Lauralkonium chloride		
Glycerin		
Dibasic sodium phosphate		
Monobasic sodium phosphate		
Sodium hydroxide		
Phosphoric Acid		
Purified water		



CAS Nº:	100299-08-9
INDICATION:	Prevention and relief of ocular itching due to allergic conjunctivitis.
DOSAGE FORM:	0.1% ophthalmic solution in a 10 ml multi-dose container
DOSAGE AND ADMINISTRATION:	1- 2 drops in each affected eye 4x/day up to 4 months.
RELATED DRUG/INDs/NDAs/DMFs:	INDs DMFs

TABLE OF CONTENTS

NDA 21-079

1. PHARMACOLOGY

1.1. OVERVIEW

Pemirolast potassium (TBX) is a mast cell stabilizer that has been demonstrated to be effective in inhibiting the antigen-induced allergic reaction in the eye of rats and guinea pigs. It has also been shown to be specific for Type I allergic reactions but not effective in Type II, III or IV hypersensitivity responses. A series of mechanism of action studies have indicated that the drug acts directly to prevent de-granulation of the mast cell in response to antigen.

1.2. MECHANISM-RELATED IMMUNOPHARMACOLOGY

Most of the submitted information on pharmacodynamic effects of TBX relating to the proposed actions was from published manuscripts. These studies were performed to assess the immuno-pharmacological properties of this agent, especially as their inhibitory effects on type I (immediate type) hypersensitivity.

1.2.1. EFFECTS ON ALLERGIC CONJUNCTIVITIS BY TOPICAL AND SYSTEMIC APPLICATIONS

1.2.1.1. Effects on Experimental Ocular Allergic Reaction. Folia Ophthalmol Jpn 1990; 41:867-870. (SR2017-P)(Vol. 1.11, p 53)

Report Nº: SR2017-P
Compound: TBX, Disodium Cromoglycate (DSCG), Amlexanox, Ketotifen, compound 48/80
Animal: ♂ Wistar Rats, six weeks of age, weighing ~200 g
Study Date: 5/1987 - 12/1998
Study Designs:

- Passive anaphylactic reaction in rat conjunctiva was induced by sensitization of rat via subconjunctival injection of anti-egg albumin rat antiserum at a dose of 50 μl/eye. Rats were challenged intravenously with a 1:1 mixture of 2.0% egg albumin and 1% Evans blue in saline to induce anaphylactic reaction 48 hr post sensitization. Animals were sacrificed 30 min post challenge, leaked dye was extracted and measured. The test compounds were given iv or topically (eye instillation) 5-15 min before induction of passive anaphylaxis.
- Compound 48/80-induced rat conjunctivitis was induced by injection of both eyes with 50 μl/eye of 0.1% solution of compound 48/80. The degree of inflammation was assessed by injection of 0.5% Evans blue in saline, 3 ml/kg before induction and measurement of leaked dye 30 min post induction. The drugs, 10 μl/eye, were instilled 2x, 5 & 15 min before induction.

Results:

- TBX, at doses 0.02 & 0.2 mg/kg iv, ↓ anaphylactic reaction in rat conjunctiva by 95.5% and 98.5%, respectively. DSCG was effective (↓90.5%) at 2.0 but not 0.2 mg/kg.
- TBX at concentrations of 0.001%, 0.01% & 0.1%, administered by eye instillation, suppressed anaphylaxis in a dose-dependent manner with values of 7.6%, 50.4% and 92.4% inhibition, respectively.
- TBX, at concentrations of 0.1% and 1.0%, blocked 48/80-induced conjunctivitis by 33.1% and 59.4%, respectively. Amlexanox (0.1% &1.0%), but not DSCG, significantly suppressed 48/80-induced inflammation by 31.9-38.6%.

1.2.1.2. Effects on Allergic Conjunctivitis in Guinea Pigs. (Vol. 1.11, p 69)

Report Nº: SR2018

Compound: TBX (Lot Nº M10): 0.01, 0.1, and 1.0%; Amlexanox: 1.0%; DSCG: 1.0 and 10%; Mepyramine: 1.0%
Animal: ♂ Hartley guinea pigs
Study Date: 3/1990
Study Designs: Allergic conjunctivitis was sensitized by subconjunctival injection with guinea pig anti-egg albumin serum (100 μl/eye). Test solution was instilled (2x, 15 & 5 min before allergic induction) in both eyes at a dose of 10 μl/eye 48 hr post sensitization. Inflammation was induced by the instillation of 12.5% egg albumin in both eyes (10 μl/eye) immediately after iv injection of 1% Evans blue (1.5 ml/kg) in the ear vein. The animals were sacrificed 30 min post challenge and the dye was extracted from the conjunctival tissues.

Results: The effects of TBX and other anti-allergic drugs on allergic conjunctivitis in guinea pigs are as follows.

Compound	Concentration (%)	Inhibition (%)
Control	-	-
TBX	0.01	12.3
	0.1	67.1**
	1.0	75.1**
Amlexanox	0.1	38.0*
	1.0	-26.6
DSCG	1.0	36.6*
	10.0	32.3
Mepyramine	1.0	60.6**

Each value represents the mean ± SE of 14 eyes; * P<0.05; ** P<0.01.

1.2.1.3. Effects on Leukocyte Migration in Allergic Conjunctivitis (PCA Reaction in Guinea Pigs). (Vol. 1.11, p 75)

Report Nº: SR2021
Compound: TBX: 0.01, 0.1, and 1.0%; DSCG: 2.0; Ketotifen: 0.1%
Dose & Route: 10 μl/topical ocular instillation, 4x/day for 2 days prior to allergy induction and 15 min and 1, 3, and 3 hr post allergy induction.
Animal: ♂ Hartley guinea pigs, 6-9 weeks old
Study Date: 11/1990 - 6/1992
Study Designs: The drug solution (10 μl) was instilled into both eyes 4x/day for two days before the induction of allergic inflammation, and 15 min before and 1, 3, and 5 hr post induction. The eosinophils and neutrophils in conjunctival tissue were evaluated 6 hr after induction of inflammation.

Results: The effects of TBX on eosinophil and neutrophil migration to the conjunctiva under allergic conditions are listed in the following table. Based on the data presented, TBX (0.01%-1.0%) inhibited eosinophil and neutrophil migration to the conjunctiva during allergic reactions.

Compound		Nº of Eye Examined	Eosinophil Counts	% Inhibition	Neutrophil Counts	% Inhibition
Vehicle Control		14	101.2 ± 9.6	-	467.1 ±39.8	-
TBX	0.001%	6	59.7 ± 19.0*	41.0	359.8 ± 79.0	23.0
	0.01%	14	31.2 ± 6.5**	69.2	291.9 ± 46.3**	37.5
	0.1%	14	29.9 ± 4.4**	70.5	265.1 ± 24.5**	43.2
	1.0%	14	27.2 ± 4.8**	73.1	170.9 ± 25.8**	63.4
DSCG	2.0%	8	33.0 ± 6.6**	67.4	153.1 ± 33.3**	67.2
Ketotifen	0.1%	8	45.3 ± 13.4**	55.2	271.5 ± 55.4*	41.9

Each value represents the mean ± SE; * P<0.05; ** P<0.01.

1.2.1.4. Effects on Allergic Conjunctivitis in Rabbits: Prolongation of Action. (SR2022)(Vol. 1.11, p 83)

Report Nº: SR2022
Study Nº: SRT-506, 055GL030, 055GL100
Compound: 0.1% TBX (Lot Nº 901214)
Animal: ♂ Japanese albino rabbits, weighing 2.5-3.5 kg, 3/group
Study Date: 2-3/1991
Study Designs: Rabbits were sensitized by the subconjunctival injection of 200 μl of anti-DNP-ascaris antiserum into each eye. A mixture of 0.4% DNP-ascaris and 1% Evans blue dye was iv injected into an ear vein. The drug solution (0.1%, 50 μl) was instilled in both eyes 1, 3, or 6 hr before the induction of allergic inflammation in the Experiment I and 0.5, 8.0, or 24 hr before allergic induction in the Experiment II. The animals were sacrificed 30 min post induction of allergic reaction and the drug effect was evaluated.

Results: Based on the results presented in the following table, the anti-allergic effect of 0.1%TBX persisted for 8 hr.

Drug	EXPERIMENT I		EXPERIMENT II	
	Instillation Time (hr)*	% Inhibition	Instillation Time (hr)	% Inhibition
Control Vehicle	1.0	-	1.0	-
0.1 % TBX	1.0	55.2**	0.5	30.4*
	3.0	73.3**	8.0	42.9**
	6.0	64.7**	21.0	13.4

* Hour Before Allergic Induction; * $p<0.05$; ** $P<0.01$.

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1.2.1.5. Effects on Allergic Conjunctivitis in Rats by Intravenous Injection. (SR2026)(Vol. 1.11, p 98).

Report Nº: SR2026
Study Nº: SRT-510, 160GM250
Compound: TBX (Lot Nº M-10), DSCG (Lot Nº 01292902)
Animal: ♂ Wistar/ST Rats, 6-week of age, weighing ~250 g
Study Date: November 1992
Study Designs: Allergic conjunctivitis was sensitized by subconjunctival injection with rat anti-egg albumin serum (50 μl). TBX or DSCG was intravenously administered to rats 48 hr post sensitization. A mixture of 2% egg albumin and 1.0% Evans blue in physiological saline was given iv one min after injection of the drug. The animals were sacrificed 30 min post challenge and the dye was extracted from the conjunctival tissues.

Results: The effects of TBX administered iv on the allergic conjunctivitis are presented in the following table. TBX was more potent (~146x) than DSCG.

Compound	Dose (mg/kg)	% Inhibition	ED_{50} (mg/kg)
Vehicle Control	-	-	-
TBX	0.0002	-6.8	0.003
	0.002	43.2	
	0.02	81.6	
	0.2	91.9	
DSCG	0.02	6.2	0.437
	0.2	19.2	
	0.6	69.5	
	2.0	79.5	

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1.2.1.6. Duration of TBX Effect on Allergic Conjunctivitis in Rabbits. (Vol. 1.11, p 90)

Report Nº: SR2524
Study Nº: 055GO180

Compound: 0.1% TBX (Lot Nº M10)
Dose and Route: 50 μl/topical ocular instillation at 0.5, 1, 2, 4, 6, 8, 12, or 24 hr prior to allergic induction
Animal: ♂ Japanese white rabbits, weighing ~2 kg, 4/group
Study Date: 5/9-13/1994
Study Designs: Rabbits were sensitized by the subconjunctival injection of 200 μl of anti-DNP-ascaris antiserum into each eye. TBX, 0.1% 50 μl/eye, was instilled in both eyes at 0.5, 1, 2, 4, 6, 8, 12, or 24 hr prior to allergic provocation. A 50/50 mixture of 0.4% DNP-ascaris and 1% Evans blue dye in 1.5 ml was iv injected into an ear vein to induce allergic reaction 48 hr post sensitization.

Results: Results showed that the effect of 0.1% TBX on anti-DNP-ascaris antiserum induced allergic conjunctivitis lasted for 12 hr.

1.2.2. EFFECTS ON OTHER ALLERGIC REACTIONS

1.2.2.1. Inhibitory Effects on Passive Cutaneous Anaphylaxis (PCA) in Rats and Guinea Pigs. Japan J Pharmacol, 1988, 48: 91-101. (SR2023-P)(Vol. 1.11, p 125)

Report Nº: SR2023
Animals: Wistar Rats, weighing 200-300 g; Hartley Guinea Pigs, weighing 350-450 g

Results: In rats, TBX, at the dose levels of 0.0025-0.025 mg/kg iv and 0.01-0.1 mg/kg po, was shown to inhibit IgE/IgG$_a$-mediated homologous PCA 200x and several thousand times more effective than Disodium Cromoglycate (DSCG) (0.5-5 mg/kg iv) and tranilast (50-250 mg, po), respectively. At the dose levels of 0.05 and 0.25 mg/kg iv, TBX caused a significant reduction on PGE_1 induced skin reaction but had no effects on extravasation of Evans blue dye induced by histamine, serotonin and bradykinin. The effects of TBX on 8-day IgE/IgGα-mediated PCA in guinea pigs are presented as followings:

Compound	Dose (mg/kg)	Route	Animal Species	% Inhibition
TBX	0	iv	Guinea Pig	-
	0.25			39.5
	1			45.3
	5			69.8
Disodium Cromoglycate (DSCG)	10			28.5
TBX	0	po	Guinea Pig	-
	5			42.6
	10			60.9
	25			63.3
	50			76.3
Tranilast	250			41.4

The ID_{50} values for TBX, DSCG and Tranilast in rat and guinea pig homologous PCA are listed in the following table.

Animal Species	Ab-Mediated PCA	Route	ID_{50} or % Inhibition		
			TBX (μg/kg)	DSCG (mg/kg)	Tranilast (mg/kg)
Rat	Rat IgE (48-hr PCA)	iv	7	1.3	-
		po	27	-	101.7
	Rat IgG_a (3-hr PCA)	iv	6	1.1	-
		po	107	-	250 (24.2%)
Guinea Pig	Guinea Pig IgE (8-day PCA)	iv	920	10 (28.5%)	-
		po	6800	-	250 (41.4%)

1.2.2.2. Effects of Pemirolast Potassium (TBX), a New Anti-allergy Drug for Oral Use, on Experimentally Induced Allergic Rhinitis in Rats and Guinea Pigs. Appl Pharmacol. 1992; 44 (6) 675-678. (92016)(Vol. 1.11, p 136)

Report Nº: 92016
Compound: TBX (Lot Nº M-13) and Tranilast
Animal: ♂ Jcl:SD Rats, 7-week of age and ♂ Hartley guinea pigs, 5-6 weeks old

Results:

- TBX, 0.1-10 mg/kg po 1 hr prior to Ag challenge - ↓ (63.2-78.1% at 0-10 min post Ag challenge and 51-76% at 0-40 min post Ag challenge) IgE-mediated increase in nasal capillary permeability in rats.
- TBX, 100 mg/kg po - significantly ↓ (up to 68.2%) IgG_1-mediated increase in nasal resistance in guinea pigs.

1.2.2.3. Inhibitory Effects on Histamine Release from Peritoneal Mast Cells and Lung Fragments of Rats. Jpn J Pharmacol 1988; 48: 103-112. (SR2024-P)(Vol. 1.12, p 8)

Report Nº: SR2024-P
Study Nº: SRT-508
Animal: Wistar-Rats

Results:

- TBX (0.1 μg/ml) ↓ (~85%) histamine release from peritoneal exudate cells (PEC) collected from homologous IgE sensitized rats.
- TBX ↓ compound 48/80 (a mast cell degranulator)-induced histamine release from normal rat PEC, but had no effect on ionophore A23187 induced release of histamine by mast cells.
- TBX, at the concentration of 10^{-3} g/ml, significantly ↓ intracellular cyclic AMP levels in normal rat PEC.
- TBX, at concentrations of 10^{-4}-10^{-6} g/ml, moderately ↓ antigen-induced histamine release from lung fragments of rats immunized with DNP-Ascaris (DNP-As) extract.

1.2.2.4. Inhibition of Chemical Mediator Release from Human Leukocytes and Lung Fragments and Lung Fragments from Actively and Passively Sensitized Guinea Pigs by TBX. Jpn J Allergy 1988; 37: 438-447. (SR2025-P)(Vol. 1.12, p 18)

Report Nº: SR2025-P
Study Nº: SRT-509
Animal: Humans and Hartley Guinea Pigs

Results:

- TBX, at 10^{-3}M, ↓ (74.9%) antigen-induced histamine release from peripheral leukocytes of patients with mite sensitive asthma.
- TBX, at $\geq 10^{-4}$M, caused a dose-dependent inhibition of anti-human IgE-induced histamine and SRS-A (slow reacting substance of anaphylaxis) release from passive sensitized human lung fragments.
- TBX, at $\geq 10^{-3}$M, ↓ antigen induced histamine and SRS-A release from either active or passive sensitized guinea pig lung fragments.

1.2.2.5. Inhibitory Effects on Histamine Release from Lung fragments and Bronchoconstriction in Guinea Pigs. Jpn J Pharmacol 1989; 51: 83-92. (SR2519-P)(Vol. 1.11, p 153)

Results: Histamine release from lung fragments of passive sensitized guinea pig was inhibited by TBX and tranilast in a dose-dependent fashion. In an *in vivo* study, guinea pigs were first passively sensitized with iv anti-DNP-As IgE serum, and 48 hr later were then challenged with aerosolized DNP-BSA. Tidal volume was measured. Oral administration of TBX, 50 and 100 mg/kg, either 2 or 8 hr before antigen challenge was able to block antigen inhalation-induced experimental asthma significantly. TBX, at 1 & 10 mg/kg iv, also suppressed both platelet activating factor (PAF)-induced bronchoconstrction in normal guinea pigs and PAF-induced platelet aggregation *in vitro*.

1.2.2.6. Effects on Type II to IV Allergic Reactions and Immunological Functions in Animal Models. Jpn J Pharmacol 1989; 51: 93-100. (SR2520-P)(Vol. 1.12, p 114)

Results:

Type II Hypersensitivity: Antibody Mediated

- Systemic Forssman Shock in ♂ guinea pigs - No effect at 1, 5, 25 mg/kg iv.
- Reverse Cutaneous Anaphylaxis in ♂ rats - No effect at 0.01, 0.05, 0.25 mg/kg iv.

Type III Hypersensitivity: Immune Complex Mediated

- Passive Arthus Reaction in ♂ guinea pigs and ♂ rats - No effect.

Type IV (Delayed Type) Hypersensitivity: T-cell Mediated

- DTH in ♂ Guinea pigs - No effect.

Antibody/Mitogen Responses:

- No effects on antibody titers to SRBC and DNP-ovalbumin in rats.
- At concentrations of ≤1 μg/ml, TBX had no effects on spleen cells from normal mice response to mitogen (Con A, PHA-P, LPS, and PWM) stimulation.

1.2.2.7. Inhibitory Effect of Pemirolast Potassium (TBX) on Release of Histamine and Leukotriene (LT) D_4 and B_4 and on Production of Platelet Activating Factor (PAF). Appl Pharmacol. 1993; 46(4): 265-271. (93017)(Vol. 1.12, p 1)

Results:

- TBX (10^{-6}-10^{-3} M) caused dose-dependent ↓ in antigen-induced release of histamine, LTD_4 and LTB_4 from lung fragments of anti-OVA passive sensitized guinea pigs.
- TBX (10^{-8}-10^{-6} M) induced a dose-related ↓ of antigen-induced PAF by peritoneal exudate cells from rats that had passively sensitized with autologous anti-serum against dinitrophenylated ascaris extract.

1.2.2.8. Effects of TBX on Histamine Migration and Leukotriene Production on the Exfoliative Slice of Nasal Allergic Membrane Epithelium Caused by Antigen. Jpn J Allergol. 1992; 41(8): 472. (92013)(Vol. 1.12, p 54)

Results:

- TBX (10^{-6}-10^{-4} M) caused dose-dependent ↓ in dust mite antigen-induced histamine migration in the inferior nasal concha exfoliate slice with values of 11.4, 18.2 and 50.0% at the concentrations of 10^{-6}, 10^{-5}, and 10^{-4} M, respectively.
- TBX (10^{-6}-10^{-4} M) induced a dose-related ↓ of antigen-induced leukotriene production by the inferior nasal concha exfoliate cells with values of 20.6, 24.4 and 60.0% at the concentrations of 10^{-6}, 10^{-5}, and 10^{-4} M, respectively.

1.2.2.9. Inhibitory Effect of Pemirolast, a Novel Anti-allergic Drug, on Leukotriene C_4 and Granule Protein Release from Human Eosinophils. Int Arch Allergy Appl Immunol. 1994; 103: 405-409. (94006)(Vol. 1.12, p 58)

Results:

- TBX (10^{-6}-10^{-3} M) caused dose-dependent ↓ (up to 77%) in A23187-induced LTC_4 release by the eosinophils.
- TBX (10^{-5}-10^{-3} M) caused dose-dependent ↓ (up to 42%) in A23187-induced eosinophil cationic protein (ECP) release by the eosinophils.
- TBX (10^{-6}-10^{-3} M) caused dose-dependent ↓ (up to 77%) in PAF and FMLP[1] induced LTC_4 release by the eosinophils.

1.2.2.10. Effects on Activation of Rat Peritoneal Mast Cells: Inhibition of Exocytotic Response and Membrane Phospholipid Turnover. Int Arch Allergy Appl Immunol 1991; 96: 62-67. (91031)(Vol. 1.12, p 62)

Results: The following findings were from the experiments conducted with rat peritoneal mast cells:

- ↓ antigen-induced conversion of phosphatidyllinosital 4,5-biphosphate (PI) to the second messenger 1,2-diacylglcerol (1,2-DG), and phosphatidylcholine (PC) to phosphatidic acid (PA);
- A dose-related ↓ of antigen-induced 1,2 DG formation and AA liberation;
- ↓ the release of 5-hydroxytryptamine (5-HT);
- blocked 48/80-induced 1,2-DG and PA formation.

1.2.2.11. Effects of Anti-allergy Drug, Pemirolast Potassium, on Phospholipase d Activation in Antigen-Stimulated Rat Basophilic Leukemia (RBL-2H3) Cells. Allergy 1995; 44 (6): 626-629. (95044)(Vol. 1.12, p 68)

Results: TBX (1.0-10 μg/ml) dose-dependently inhibited the Ag-induced (DNP-As), but not PMA (phorbol myristate acetate) or A23187-induced activation of phospholipase D (PLD) in rat basophilic leukemic cells by measuring the production of phosphatidylethanol.

1.2.2.12. An Anti-allergic Drug, Pemirolast Potassium, Inhibits Inositol 1,4,5-Trisphosphate (IP_3) Production and Ca^{2+} Mobilization in Antigen-Stimulated Rat Basophilic Leukemia (RBL-2H3) Cells. Jpn J Allergol. 1994; 43 (2): 142-151. (94017)(Vol. 1.12, p 88)

Results: TBX (1.0-10 μg/ml) caused dose-dependent ↓ of:

- Ag-induced degranulation by measuring serotonin ([C^{14}]5-HT) release in RBL-2H3 cells;
- the formation of IP_3 as the results of ↓ activation of phosphalipase C in RBL-2H3 cells;

[1] PAF = Platelet Activating Factor; FMLP = formyl-methionyl-leucyl-phenyl-alanine.

- Ag-induced Ca^{2+} mobolization in RBL-2H3 cells;
- AA release in RBL-2H3 cells; and
- 1,2-DG and PA (phosphatidic acid) production.

1.2.2.13. Effect of TBX on Ca Uptake into Rat Peritoneal Mast Cells. (SR2538)(Vol. 1.12, p 98)

A–Study on the Antiallergic Effect of TBX - Its Effect Against Ca^{2+} in Mast Cells. (SR2539)(Vol. 1.12, p 105)

Report Nº: SR2538 & SR2539
Compound: TBX (Lot Nº M-11), DSCG, compound 40/80, and $^{45}CaCl_2$
Animals: ♂ Wistar rats, weighing 200-300 g were used for the source of peritoneal mast cells
Study Date: 4/4-20/1990 for SR2538; 10/20/1989-4/20/1990 for SR2539

Results: Various concentrations of TBX were added to rat peritoneal mast cells with compound 40/80 simultaneously. Influx of ^{45}Ca and the changing of Ca^{2+} levels (using quin2, a Ca^{2+} sensitive fluorescent indicator) in the mast cells were assessed to elucidate the suppressive mechanism of TBX on the release of chemical mediators. Results from both studies showed that TBX inhibited the compound 40/80 induced inflow of Ca and the increase of fluorescence intensity of quin-2 in mast cells. It appeared that TBX was 100x more potent than DSCG on the inhibition of Ca influx. Mean percentage inhibitions of ^{45}Ca influx are listed in the following table.

Compound	Concentrations (μg/ml)	Compound 40/80 (1.0 μg/ml)	Mean % ↓ of ^{45}Ca Uptake	Mean % ↓ of fluorescence Intensity
Control	-	+	0	0
TBX	10	+	83.5	-
	1	+	89.0	45
	0.1	+	83.8	26
	0.01	+	47.9	9
	0.001	+	31.1	-
DSCG	100	+	82.5	-
	10	+	-	26

1.2.3. SUMMARY OF ANTI-ALLERGIC EFFECTS OF TBX

Results from *in vivo* and *in vitro* pharmacology studies related to the anti-allergic properties of TBX are summarized in the following two tables.

IN VIVO STUDIES			
Species Nº/Group	Doses	Route	Findings
Wistar rat 18♂/group	0.001, 0.01 0.1, 1%	Topical (Ocular)	TBX caused a dose-dependent ↓ of the allergic response with an ED_{50} of 0.01%. Higher doses of TBX were needed for non-allergic reactions.
Hartley guinea pig 14♂ /group	0.01, 0.1, 1	Topical (Ocular)	TBX induced a dose-dependent ↓ of the allergic reaction with a 67% inhibition at 0.1%.
Hartley guinea pig 6-14♂ /group	0.001, 0.01, 0.1, 1%	Topical (Ocular)	TBX dose-dependently ↓eosinophil and neutrophil migration to conjunctiva during allergic reaction up to 73.1% and 63.4% inhibition, respectively.
Jpn albino rabbit 6♂ /group	0.1%	Topical (Ocular)	TBX prevented Ag-induced allergic inflammation up to 8 hours post a single application.
Jpn albino rabbit 4♂ /group	0.1%	Topical (Ocular)	TBX significantly inhibited an allergic response when it was administered 0.5 - 12 hr prior to the challenge. The greatest inhibition was observed at 2 hr prior to the challenge.
Wistar rat 16♂/group	0.02, 0.2 mg/kg	iv	TBX at 0.02 mg/kg induced 95% inhibition of the allergic response.
Wistar rat 10♂/Group	0.0002, 0.002, 0.02, 0.2 mg/kg	iv	TBX induced a dose-dependent inhibition of allergic reaction, with an ED_{50} of 0.003 mg/kg.

IN VITRO STUDIES				
Species	Tissue	Compound	Dose	Observations
♂ Hartley guinea pig	Tracheal rings	TBX	10^{-10}-10^{-4} g/ml	TBX inhibited leukotriene but not histamine or methacholine induced contraction.
♂ Wistar rat	Peritoneal exudate cells	TBX DSCG tranilast	10^{-10}-10^{-4} g/ml 10^{-7}-10^{-4} g/ml 10^{-6}-10^{-4} g/ml	TBX, DSCG, and tranilast inhibited the release of histamine to the antigen challenge, all with maximum inhibition of ~ 85 %. TBX was ~100x more potent than DSCG and ~1000x more potent than tranilast.
♂ Wistar rat	Peritoneal exudate cells	TBX	10^{-8}-10^{-7} g/ml	Inhibitory effects on histamine release were not affected by the deficiency of glucose, were reduced by the presence of D_2O, and by the absence of calcium in the medium.
♂ Wistar rat	Peritoneal exudate cells	TBX DSCG tranilast	10^{-10}-10^{-5} g/ml 10^{-7}-10^{-5} g/ml 10^{-7}-10^{-5} g/ml	TBX was most potent in inhibition of the release of histamine induced by compound 48/80 but not A23187.
♂ Wistar rat	Peritoneal exudate cells	TBX isoproterenol theophylline	10^{-4}-10^{-3} g/ml $2x10^{-6}$ g/ml 10^{-3} g/ml	TBX isoproterenol and theophylline increased an intracellular level of cyclic AMP.
♂ Wistar rat	Lung fragment	TBX DSCG theophylline	10^{-3} g/ml 10^{-3} g/ml $5x10^{-4}$ g/ml	TBX and DSCG non-competitively inhibited cyclic AMP-dependent phosphodiesterase, with Ki values of $8.7x10^{-4}$M and $3.25x10^{-3}$ M, respectively. Theophylline displayed a competitive inhibition, with a Ki value of $2.5x10^{-4}$ M .
human	Leukocytes	TBX tranilast theophylline	10^{-5}-10^{-2} M 10^{-5}-10^{-3} M 10^{-5}-10^{-3} M	TBX ($\geq 10^{-4}$M) caused dose-dependent inhibition of antigen-induced histamine release.
human	Lung fragment	TBX DSCG tranilast	10^{-7}-10^{-2} M 10^{-7}-10^{-2} M 10^{-7}-10^{-3} M	TBX ($\geq 10^{-6}$M) dose-dependently inhibited antigen-induced release of histamine and SRS-A.
♂ Hartley guinea pig	Lung fragment	TBX DSCG	10^{-6}-10^{-2}M 10^{-4}-10^{-2}M	TBX but not DSCG ↓ the release of histamine and SRS-A.
♂ Hartley guinea pig	Lung segment	TBX tranilast	10^{-6}-10^{-2}M 10^{-6}-10^{-3}M	TBX and tranilast inhibited the release of histamine. TBX was more potent than tranilast.
Wistar rat	Peritoneal mast cells	TBX	10^{-7}-10^{-5} g/ml	TBX at the concentrations tested effectively inhibited degranulation in response to antigen and compound 48/80; suppressed the formation of 1,2-diacylglycerol and phosphatidic acid and the decrease of phospholipase A_2.

1.3. SAFETY PHARMACOLOGY

1.3.1. OCULAR-RELATED EFFECTS

1.3.1.1. Effects of TBX Ophthalmic Solution on Pupil Diameter. (SR2019)(Vol. 1.11, p 105)

Report Nº: SR2019
Compound: 0.1% Pemirolast Potassium (Lot Nº M-10), 0.05% Ketotifen Fumarate, 2% DSCG, and 0.25% Amlexanox
Dose and Route: 50 μl/ocular topical instillation, 4x at 5-min intervals
Negative Control: Saline
Positive Control: 0.05% Cyclopentolate
Animal: ♂ Japanese albino rabbits, weighing 2.5-3.0 kg, 3/group
Compliance with GLP/QAU: N/A
Study Date: September 1989

Results: TBX (0.1% & 1.0%), 2% DSCG and 0.25% Amlexanox had no effect on pupil diameter at 15-120 min post instillation. Ketotifen, 0.05%, had a mild mydriatic effect at 30-60 min post instillation. Contrarily, 0.05% Cyclopentolate caused profound mydriasis (an ↑ in pupil diameter) at 15-60 min after instillation.

1.3.1.2. Effects of TBX Ophthalmic Solution on Pupil Diameter II. (SR2028)(Vol. 1.11, p 112)

Report Nº: 2028

Study Nº: SRT-512, 049MM130
Compound: 1.0% Pemirolast Potassium (Lot Nº M-10)
Dose & Route: 50 μl/ocular instillation, 4x at 5-min intervals.
Negative Control: Saline
Positive Control: 0.05% Cyclopentolate
Animal: ♂ Japanese albino rabbits, weighing 2.5-3.0 kg, 5/group
Compliance with GLP/QAU: N/A
Study Date: November 1992

Results: TBX (1.0%) had no effect on pupil diameter, measured with a Haab pupillometer under 300 lux constant light, at 15-120 min post instillation. Positive control, 0.05% Cyclopentolate, induced marked mydriasis at 15-60 min after instillation.

1.3.1.3. Effects of TBX Ophthalmic Solution on Corneal Sensory Reactions. (SR2020)(Vol. 1.11, p 118)

Report Nº: SR2020
Compound: 0.1% Pemirolast Potassium (Lot Nº M-10), 0.05% Ketotifen Fumarate, 2% DSCG, and 0.25% Amlexanox
Dose and Route: 10 μl/ocular instillation 4x at 1-min intervals.
Negative Control: Saline
Positive Control: 0.05% Oxybuprocaine
Animal: ♂ Hartley guinea pigs, weighing ~350 g, 5/group
Compliance with GLP/QAU: N/A
Study Date: August 1989

Results: 0.1% TBX, 2% DSCG and 0.25% Amlexanox had no local superficial anesthesia effect as blink reflex did not disappear during 45 min post instillation. Contrarily, 0.05% Ketotifen and positive control, 0.05% Oxybuprocaine, had significantly reduced blink reflex at 15-30 min after instillation.

1.3.2. OTHER EFFECTS:

The following table summarized findings of a variety studies performed to evaluate the effects of TBX on CNS, respiratory and circulatory system, autonomic nervous system, and platelet coagulation functions.

Test	Species	Route	Dose (mg/kg)	Results
General Signs	♂ Mouse (N=5)	po	10, 100	No effect within 5 hr
CNS				
Spontaneous motor Activity	♂ Mouse (N=5-8)	po	1, 10, 100	1 mg/kg: No effect, 5 hr; ≥10 mg/kg: transit slight inhibition within 30 min.
EEG	♂ Rabbit (N=3-4)	iv	0.1, 1, 20	≥1 mg/kg: slight somnolence, 5-30 min post dose
Potentiation of Anesthesia	♂ Mouse (N=10)	po	1,10, 100	↔
Electric, Pentetrazol, & Strychnine Seizure	♂ Mouse (N=5)	po	1,10, 100	↔
Brewer's Yeast-Induced Hyperthermia	♂ Rat (N=6)	po	1,10, 100	≥1 mg/kg: antipyretic effect
Prostaglandin $E_{2\alpha}$-Induced Hyperthermia	♂ Mouse (N=5)	po	1,10, 100	↔
LPS-Induced Hyperthermia	♂ Rabbit (N=3-5)	po	1,10, 100	No Effect within 5 hr
Analgesic Effect (Acetic Acid Writhing Test)	♂ Mouse (N=9)	po	1,10, 100	↔
Motor Coordination (Rotar Rod)	♂ Mouse (N=5)	po	1,10, 100	No Effect within 5 hr
Somatic Nerve System				
Local Anesthesia (Corneal Reflex)	♂ Guinea Pig (N=5)	io	0.1%	No effect within 30 min.
Diaphragmatic Neuromuscular Preparation	♂ Rat (N=3)	bath	10^{-4}-10^{-3} g/ml	10^{-3} g/ml: ↑ contraction to stimulation of nerve and muscle
Respiratory and Circulatory Systems				
Respiration, Blood Pressure, Heart Rate, Blood Flow	♂ & ♀ Dog (N=3)	iv	0.01, 0.1, 1, 20	≥1 mg/kg: ↓ BP ↑ HR & ↑ blood flow in femoral artery; transit slight ↓ respiration
ECG (Lead II)	♂ & ♀ Dog (N=3)	id, iv	i.d.: 10 ,100 i.v.:1, 20	↔
Isolated Atria	♂ Guinea Pig (N=6-9)	bath	10^{-6}-10^{-3} g/ml	≥10^{-5} g/ml: ↑ rate and contraction, dose-dependent
Autonomic Nervous System				
Isolated Ileum				
Spontaneous Contraction	♂ Rabbit (N=7)	bath	10^{-7}-10^{-3} g/ml	≥10^{-5} g/ml: ↑ contraction; 10^{-3} g/ml: ↑ contraction, ↓ frequency of contraction
Acetylcholine, Histamine, Serotonin, $BaCl_2$, and Bradykinin Contraction	♂ Guinea Pig (N=3-13)	bath	10^{-7}-10^{-3} g/ml	≥10^{-4} g/ml: induced a contraction of cholinomimetic mechanism
Isolated Trachea:				
Restin Tension	♂ Guinea Pig (N=4-7)	bath	10^{-5}-10^{-1} g/ml	≥10^{-5} g/ml: ↓ tension dose-dependently
Acetylcholine, Histamine, Serotonin, $BaCl_2$, and Bradykinin Contraction				≥10^{-5} g/ml: ↓ contractions to the agonist dose-dependently
Isolated Uterus				
Oxytocin & Spontaneous Contraction	♀ Rat (N=3-6)	bath	10^{-6}-10^{-3} g/ml	10^{-3} g/ml: ↓
Uterus Spontaneous Contraction in Situ	♀ Rat (N=4-7)	iv	0.01, 0.1, 1	≥0.1 mg/kg: slight ↓
Isolated Vas Deferens Contraction by Norepinephrine	♂ Rat (N=3)	bath	10^{-6}-10^{-3} g/ml	10^{-3} g/ml: slight ↓
Isolated Blood Vessel Contraction by Norepinephrine	♂ Rat (N=9)	bath	10^{-7}-10^{-3} g/ml	≥10^{-4} g/ml: dose dependent relaxation
Gastrointestinal Transport (Charcoal Loading)	♂ Mouse (N=5)	po	1, 10, 100	↔
Pupil	♂ Mouse (N=5)	po	1, 10, 100	↔
Contraction of Nictitating Membrane	♂ & ♀ Cat (N=3)	iv	1	No effect within 3 hr
Gastric Secretion (Pylorus Ligation)	♂ Rat (N=9-11)	id	1, 10, 100	100 mg/kg : inhibited secretion of gastric juice, acid, and pepsin
Antinuclear Effect (Shay Ulcer)	♂ Rat (N=5-9)	id	1, 10, 100	↔
Test	**Species**	**Route**	**Dose (mg/kg)**	**Results**
Other Effects				
Anti-inflammatory (Carrageenin Edema)	♂ Rat (N=6)	po	1, 10, 100	↔
Diuretic effect & PSP Test	♂ Rat (N=6-9)	po	1, 10, 100	100 mg/kg: ↑ K^+ excretion; ↓ PSP excretion
Liver Function (BSP test)	♂ Rat (N=6)	po	1, 10, 100	↔
Blood Coagulation	♂ Rat (N=4-7)	po	1, 10, 100	↔
Gastrointestinal Tract	♂ Rat (N=5)	po	1, 10, 100	↔
Platelet Coagulation: ADP, Collagen, Arachidonic Acid (AA)	♂ Rat (N=3-4)	cell culture	10^{-5}-10^{-2} g/ml	≥10^{-3} g/ml: ↓ ADP; ≥3x10^{-4} g/ml: ↓ Collagen; ≥10^{-3} g/ml: ↓AA
PAF	♂ Guinea pig			≥3x10^{-4} g/ml: ↓

id = Intraduodenal; io = intraocular; PSP = Phenolsulfonphthalein; BSP = Bromsuphalein; ↔ = No effect

1.3.2.1. References

1. Santen Ltd. Study Report. Pharmacologic Properties of BMY-26517. (SR2105)(Vol. 1.11, p 163)
2. General Pharmacological Study of TBX. Pharmacol Treat 1989; 17 (4): 1249-1279. (89007)(Vol. 1.12, p 122)

1.3.3. RECEPTOR BINDING

Radioligand binding studies with rat brain membrane receptor systems demonstrated that TBX had little or no affinity for α_1-adrenergic, ß-adrenergic, muscarinic, cholinergic, histamine H_1, or dopamine D_2 receptors.

2. ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

2.1. OCULAR ADME

2.1.1.1. Ocular Penetration and distribution of Pemirolast Potassium Ophthalmic Solution after Topical Applications in the Rabbits. Folia Ophthalmol Jpn 1990; 41: 2095-2100. (Vol. 1.12, p 208)

Report Nº: SR2029-P
Study Nº: SRT-601
Compound: Pemirolast Potassium (Lot Nº M-10): 0.1%, pH 8.0
Dose: 50 μl of 0.1% TBX , instillation
Animal: 32 Japanese male albino rabbits, weighing 2.4-2.9 kg, 4/group
Compliance with GLP/QAU: Not indicated.
Study Designs: TBX (0.1%, 50 μl) was instilled into right eye of each rabbit. Blood was collected from the articular artery of the rabbits at 0.25, 0.5, 1, 2, 4, 8, 24, and 72 hr after ophthalmic instillation with TBX. After the blood was taken, the rabbits were sacrificed. The palpebral and bulbar conjunctiva were dissected, aqueous humor was collected, and the eye was excised and rapidly frozen with liquid N_2. The levels of TB (free acid) in the plasma and ocular tissues were determined with an established HPLC method.

Results: Mean plasma concentrations (ng/ml) and ocular tissue distribution of TB (free acid, ng/g) at 0.25 - 72 hr post instillation are listed in the following table. Higher concentrations of TB were found in extra-ocular tissues (palpebral conjunctiva, bulbar conjunctiva, cornea, and anterior sclera) than in intraocular tissues. Drug levels in the tissue and plasma declined over time. However, high levels of TB remained in the palpebral and bulbar conjunctival 24 hr post instillation. In contrast, plasma TB levels were not detectable by 4 hr post instillation of the drug.

Tissues Samples	Concentration of TBX (ng/ml or ng/g)							
	0.25 hr	0.5 hr	1 hr	2 hr	4 hr	8 hr	24 hr	72 hr
Palpebral Conjunctiva	11801.8 (705.3)[a]	673.5 (188.9)	659.1 (253.8)	1485.1 (795.0)	1141.9 (352.8)	1598 (972.3)	870.2 (517.4)	106.6 (61.7)
Bulbular Conjunctiva	4020.8 (1121.5)	1109.3 (307.8)	780.1 (224.1)	1543.2 (542.9)	1011.0 (339.9)	519.5 (189.8)	510.2 (216.4)	57.1 (42.6)
Cornea	2347.8 (54.6)	1545.4 (251.4)	477.8 (61.1)	237.4 (43.5)	60.2 (6.9)	12.6 (1.5)	9.5 (4.8)	-[b]
Aqueous Humor	287.6 (72.4)	328.6 (61.0)	202.0 (34.5)	109.6 (20.5)	12.8 (3.7)	1.7	-	-
Iris/Ciliary Body	282.6 (48.0)	313.8 (29.0)	140.6 (30.9)	84.0 (15.0)	7.3 (1.3)	1.9 (0.3)	3.3 (0.7)	-
Anterior Sclera	2639.4 (800.1)	1174.4 (256.1)	219.5 (40.8)	205.1 (61.8)	65.1 (26.4)	13.5 (4.5)	9.4 (5.1)	6.4
Lens	5.5	1.8	1.7	3.9 (0.9)	1.6 (0.2)	1.5 (0.3)	2.0	-
Retina/Choroid	63.4 (32.5)	27.5 (8.3)	16.1 (6.3)	15.1 (4.6)	4.2 (1.2)	1.6 (0.5)	-	2.9
Posterior Sclera	134.1 (54.3)	95.3 (30.7)	57.6 (15.0)	37.8 (13.2)	21.4 (10.2)	5.6 (1.8)	4.1	1.9
Plasma	12.4 (1.5)	3.9 (0.5)	3.0 (0.6)	1.6 (0.3)	-	-	-	-

[a] Values in the parenthesis represented standard error of mean; [b] Values < 1.0 ng/ml or ng/g (detection limit).

2.1.1.2. Ocular Penetration and distribution of Pemirolast Potassium Ophthalmic Solution after Repeated Topical Applications in the Rabbits. (Vol. 1.12, p 221)

Report Nº: SR2033
Study Nº: SRT-605
Compound: Pemirolast Potassium (Lot Nº M-10), 0.1 %
Animal: Japanese male albino rabbits, weighing 2.0-3.0 kg, 5/group
Compliance with GLP/QAU: Not indicated.
Study Designs: TBX (0.1%) was instilled into the conjunctival sac of each eye of rabbits once only or twice daily for a total of either 7 or 13 times. The levels of TBX in blood, palpebral and bulbar conjunctiva, and aqueous humor were measured according to the following schedule:

- 3, 6, 12, 24 and 72 hr after a single instillation
- 3, 6, and 12 hr after 7 instillation
- 3, 6, 12 hr after 13 instillation

Results: Mean TB (free acid of TBX) concentrations in conjunctiva and aqueous humor after single and multiple instillation are presented in the following table. Calculated $T_{½}$ for single instillation was 15.4 hr. TBX was not detectable in the aqueous humor 12 hr post either single or multiple (7 & 13 times) instillation. TBX levels reached a steady state after 7 instillation by the evidence that similar concentrations were measured after 7 and 13 repeated instillation. After repeated instillation (7 & 13 times), the concentrations of TB in conjunctiva and aqueous humor decreased over time, suggesting that TB might not accumulate in the ocular tissues.

Sampling Site	Instillation Frequency	Concentration of TBX (ng/ml)					
		1 hr	3 hr	6 hr	12 hr	24 hr	72 hr
Palpebral Conjunctiva	1	ND[a]	954.7 ± 179.8	559.5 ± 389.7	462.9 ± 139.9	278.4 ± 93.3	26.2 ± 10.1
	7	ND	2019.1 ± 1176.9	1688.7 ± 1072.2	1112.4 ± 715.5	ND[a]	ND
	13	ND	1900.6 ± 701.5	1097.8 ± 510.6	1012.1 ± 821.5	ND	ND
Bulbar Conjunctiva	1	ND	1071.1 ± 306.2	606.0 ± 341.5	445.4 ± 153.2	248.5 ± 50.3	30.4 ± 19.6
	7	ND	2208.7 ± 1161.4	1623.4 ± 725.8	1017.4 ± 381.1	ND	ND
	13	ND	1930.4 ± 392.1	1604.1 ± 620.5	1038.5 ± 356.7	ND	ND
Aqueous Humor	1	457.8 ± 130.0	61.5 ± 33.8	5.6 ± 1.2	-[b]	-	-
	7	ND	80.9 ± 41.9	8.9 ± 8.0	-	ND	ND
	13	ND	86.0 ± 21.5	7.5 ± 6.1	-	ND	ND

[a] ND = Not Done ; [b] Values < 1.0 ng/ml or ng/g (detection limit).

2.1.1.3. Retainability of Pemirolast Potassium in bulbar Conjunctiva in Albino Rabbits after Topical Applications of 0.1% Pemirolast Potassium Ophthalmic Solution. (Vol. 1.12, p 230)

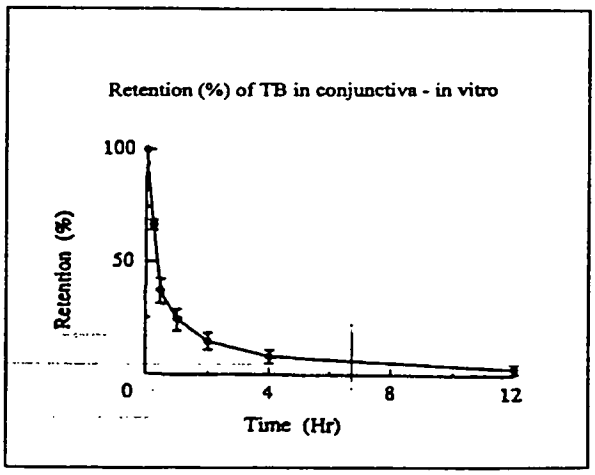
Report Nº: SR2034
Study Nº: SRT-606, 088DN040
Compound: Pemirolast Potassium (TBX), 0.1% (Lot Nº D-2); N-acetylcysteine (NAC), 20%
Animal: Japanese male albino rabbits, weighing 2.0-3.0 kg, 5/group
Compliance with GLP/QAU: Not indicated.
Study Date: 3/1993
Methods:

- *In Vivo* - NAC (20%, 25 μl) was instilled (a total of 3x, at 5-min intervals) into the lower palpebral conjunctival sac of the left eye and physiological saline into the right eye at -20, -15, and 10 min prior to administration of 0.1% TBX (50 μl) into both lower conjunctival sac of both eyes. The rabbit was sacrificed 6 hr post instillation of TBX, the bulbar conjunctival was isolated, and TB concentrations were determined.
- *In Vitro* - The bulbar conjunctiva was isolated from normal rabbit and immersed in 0.1% TBX. The uptake of TB was 1.7 μg/mg. The conjunctiva with 1.7 μg/mg TBX uptake was incubated in an artificial tear solution and the concentration of released TB in the artificial tear solution was determined with HPLC.

Results: The effect of mucin removal on TB concentrations in bulbar conjunctiva are shown as follows.

	TB Concentration (ng/g)	
	Control Eye	NAC Treated Eye
Animal Nº 1	1241.8	229.9
Animal Nº 2	616.5	395.5
Animal Nº 3	402.2	60.3
Mean ± SD	753.5 ± 436.2	228.6 ± 167.6

In the *in vitro* setting, the retention of TB by the conjunctiva decreased over time as illustrated in the right figure; at the end of 12 hr evaluation period, the retention of TB by conjunctiva was only 3.2%. Therefore, the retention of TB in conjunctiva appeared to be mucin-related.



2.1.1.4. Affinity of Pemirolast Potassium (TBX) to Melanin. (Vol. 1.12, p 239)

Report Nº: SR2030
Study Nº: SRT-602, 003CI010
Compound: Pemirolast Potassium (Lot Nº M-10), Chloroquine Diphosphate (Lot Nº 104F-0821)
Compliance with GLP/QAU: Not indicated.
Study Date: 2-4/1988
Study Designs: A melanin suspension at a concentration of 1 mg/ml was prepared from bovine eye uvea and retinal pigment epithelia. TBX-melanin binding rate was determined by the incubation of TBX (0.05 mM, final concentration) with melanin at 37°C for 8 hr. The free drug in the supernatant of the reaction mixture was assayed using a [redacted]

Results: The binding rate of TBX-melanin was much lower than that of chloroquine diphosphate-melanin (1.1 ± 0.6% vs 94.3 ± 1.6%). Therefore, TBX had little or no affinity for melanin.

2.2. SYSTEMIC ADME

2.2.1. ABSORPTION, TISSUE DISTRIBUTION AND EXCRETION

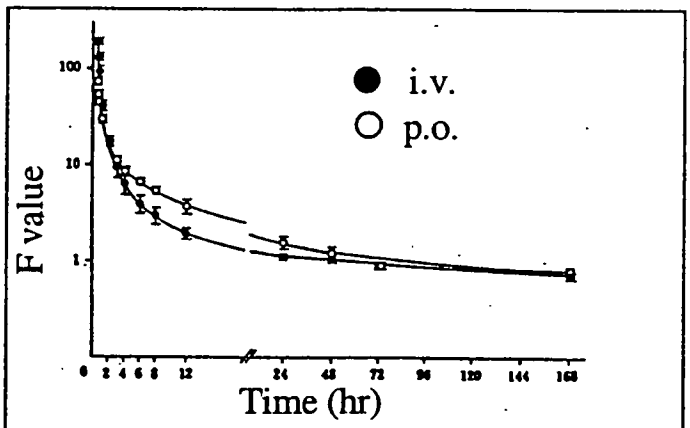
2.2.1.1. Studies on the Metabolic Fate of TBX (1): Absorption, Distribution and Excretion in Rats after Administration of [^{14}C]-TBX. Jpn Pharmacol Ther, 1989; 17: 1215-1229. (89004)(Vol. 1.12, p 245)

Compound: [^{14}C]-TBX, 46.5 mCi/mmol.
Dose/Route: 1 mg/kg single dose iv, po, or intestinal infusion
Dosing Duration: single dose
Animals:

- ♂ SD rats, 6 weeks old;
- pregnant ♀ rats (Gestation Day 18); and
- dams with pups at Post Partum Day 10.

Results:

- Radioactivity in Blood - Radioactivity was readily detected in the blood with a T_{max} of 10 min following oral administration, an indicative of rapid absorption. The relative radioactivity in the blood over the period of 168 hr after iv and oral administration of [^{14}C]-TBX was illustrated in the right figure.



F value (%) = [(Radioactivity in sample)/(Sample weight)]/ [(Radioactivity in administered fluid)/(Animal weight)] x 100

- Excretion of Radioactivity in Urine, Feces, and Expired Air - The urinary excretion was the major route of radioactivity elimination. Approximately 73% - 80% of radioactivity dose was excreted in the urine at 168 hr post oral and iv administration. Minute levels of radioactivity (~0.2%) were eliminated through expired air. The cumulative excretion of radioactivity (% dose) in urine, feces and expired

air at various time points following oral and iv administration of [^{14}C]-TBX to male rats is summarized in the following table.

Sample	Mean % Radioactive Dose (± D)							
	0-6 hr	12 hr	24 hr	48 hr	72 hr	96 hr	120 hr	168 hr
ORAL ADMINISTRATION								
Urine	56.79 ± 5.42	66.53 ± 0.74	72.16 ± 2.79	72.50 ± 2.86	72.55 ± 2.89	72.59 ± 2.91	72.62 ± 2.92	72.63 ± 2.92
Feces	0.01 ± 0.01	0.01 ± 0.01	20.51 ± 2.08	21.19 ± 2.00	21.28 ± 1.95	21.33 ± 1.93	21.36 ± 1.92	21.39 ± 1.92
Expired Air	0.02 ± 0.01	0.04 ± 0.02	0.06 ± 0.02	0.08 ± 0.02	0.09 ± 0.03	0.11 ± 0.04	0.14 ± 0.04	0.16 ± 0.05
Carcass	ND	ND	ND	ND	ND	ND	ND	0.65 ± 0.04
IV ADMINISTRATION								
Urine	74.75 ± 2.38	77.79 ± 2.91	79.20 ± 2.30	79.39 ± 2.33	79.44 ± 2.35	79.47 ± 2.35	79.49 ± 2.36	79.60 ± 2.36
Feces	ND	2.36 ± 3.81	16.04 ± 1.91	16.68 ± 1.90	16.75 ± 1.90	16.79 ± 1.89	16.83 ± 1.89	16.86 ± 1.89
Expired Air	0.01 ± 0.01	0.03 ± 0.02	0.05 ± 0.03	0.06 ± 0.03	0.07 ± 0.03	0.10 ± 0.04	0.11 ± 0.04	0.15 ± 0.03
Carcass	ND	ND	ND	ND	ND	ND	ND	0.51 ± 0.07

ND= Not Detected.

- Excretion of Radioactivity in Bile - The cumulative excretion of radioactivity expressed as mean % dose in bile, urine, feces after oral and iv administration, and intestinal infusion of ^{14}C-TBX to bile duct-cannulated ♂ rats is presented in the following table. In the intestine and liver re-circulation experiment, around 22% of dose was recovered again in the bile at 48 hr after the infusion. Majority of radioactivity was eliminated via the urine.

Sample	Mean % Radioactive Dose (± SD)								
	0-1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	24 hr	48 hr
ORAL ADMINISTRATION OF ^{14}C-TBX TO BILE DUCT-CANNULATED MALE RATS									
Bile	6.78 ± 0.63	11.34 ± 1.14	13.75 ± 1.26	15.12 ± 1.08	16.80 ± 1.72	17.90 ± 1.73	19.46 ± 0.96	20.65 ± 0.62	20.87 ± 0.72
Urine	NA	NA	NA	NA	43.74 ± 5.52	NA	58.93 ± 4.15	66.16 ± 1.54	67.13 ± 1.03
Feces	NA	NA	NA	NA	NA	NA	2.21 ± 0.66	3.34 ± 0.34	5.38 ± 0.93
IV ADMINISTRATION OF ^{14}C-TBX TO BILE DUCT-CANNULATED MALE RATS									
Bile	9.13 ± 1.61	12.62 ± 1.70	14.97 ± 1.51	16.47 ± 1.55	17.92 ± 1.64	18.56 ± 1.61	19.02 ± 1.62	19.33 ± 1.60	19.43 ± 1.58
Urine	ND	ND	ND	ND	72.23 ± 3.34	ND	76.26 ± 0.80	78.81 ± 1.36	79.68 ± 1.48
Feces	ND	ND	ND	ND	ND	ND	0.33 ± 0.17	0.49 ± 0.19	0.74 ± 0.37
SINGLE INTESTINAL INFUSION OF RADIOACTIVE BILE FLUID* TO BILE DUCT-CANNULATED RATS									
Bile	3.31 ± 0.98	5.62 ± 1.51	7.61 ± 2.18	9.53 ± 2.27	11.82 ± 2.26	13.60 ± 2.28	16.12 ± 1.29	20.47 ± 2.35	22.46 ± 1.42
Urine	NA	NA	NA	NA	NA	NA	13.75 ± 0.20	38.44 ± 2.95	41.16 ± 3.58
Feces	NA	NA	NA	NA	NA	NA	1.88 ± 1.70	17.92 ± 5.61	26.98 ± 1.71

ND = Not Detected; NA = Not Available; * Excreted from the other rats.

- Whole Body Macro-autoradiography -

  ♂ rats: Whole body autoradiographs revealed that high concentrations of radioactivity could be observed in the stomach, upper intestine, esophagus, and mouth membrane at 5-10 min after oral administration. In addition, strong radioactivity signals were observed in the kidney, bladder, and urethra. Significant levels of radioactivity were noted in the liver, blood, and lung at 3 hr post administration. By 24 hr post dosing, the radioactivity was only observed in the large intestinal tract.

  Pregnant ♀ (GD 18) rats: The radioactivity distribution patterns were similar to those observed in the ♂ rats. Additionally, the radioactivity could be observed in the fetuses at 3 hr post dosing.

- Tissue Distribution of Radioactivity in ♂ and Pregnant ♀ (GD 18) Rats - Highest levels of radioactivity were detected in the stomach, kidneys, liver, and small intestine at 10 min post dosing. In addition to the GI tract, high levels of radioactivity were detected in organs/tissues rich in blood contents, such as kidney, liver and lungs at 3 h post dosing. By 24 hr post dosing, except for the contents in the large intestine, the concentrations of radioactivity had decreased in all the organs and tissues. The results of radioactivity measurements were in agreement with that of the autoradiographic observations. Results from GD 18 pregnant rats showed that the radioactivity was detectable in the fetus, indicating that TBX crossed through the placenta and was available to

the fetus. However, the radioactivity in the fetal blood was much lower than that in the maternal blood. Mean (±SD) TBX concentrations expressed as ng equivalent/g tissue in the representative tissues/organs at various time points after oral administration to ♂ and pregnant ♀ are shown in the following tables.

Tissue	Mean (±SD) TBX Concentrations (ng eq/g)			
	10 min	1 hr	3 hr	24 hr
♂ RATS				
Cerebrum	49.89±7.06	48.12±3.82	25.67±0.83	2.98±1.31
Cerebellum	54.54±8.60	50.30±5.06	27.47±0.29	3.25±0.53
Pituitary	217.98±28.07	174.67±21.41	65.30±17.16	21.06±19.86
Eyeball	91.62±17.33	83.91±9.93	44.54±6.16	3.66±1.29
Thyroid	326.37±110.56	243.37±78.00	79.29±19.32	79.49±20.99
Thymus	177.57±7.26	112.67±12.39	37.04±1.97	6.78±0.57
Heart	356.94±56.79	187.82±12.49	56.72±4.20	4.41±0.94
Lung	550.20±49.30	275.20±31.31	76.22±17.65	6.20±0.90
Trachea	463.01±78.00	241.55±75.85	63.19±10.31	16.64±5.37
Liver	1945.16±247.42	1166.03±132.65	180.77±19.42	14.91±2.29
Spleen	349.64±32.66	213.65±53.10	52.02±18.42	6.48±0.56
Pancreas	661.35±187.45	343.65±41.10	71.65±19.64	13.54±1.51
Kidney	13965.37±1724.60	8418.55±914.82	631.50±70.21	11.58±3.88
Adrenal	673.20±112.55	380.98±101.52	85.86±30.74	13.81±5.84
Fat	96.90±38.04	68.18±13.76	44.18±3.04	5.45±2.53
Muscle	167.22±21.34	92.90±14.15	28.53±4.53	2.99±1.19
Bone Marrow	228.06±18.75	141.89±18.73	56.73±6.16	17.71±7.71
Stomach	24463.24±5583.74	11371.14±631.65	1161.87±485.01	32.43±19.14
Small Intestine	1584.72±332.20	5352.22±1110.49	9037.07±1611.41	35.24±18.60
Cecum	270.25±76.90	764.85±139.69	875.69±632.41	189.14±105.87
Large Intestine	702.51±226.30	1272.76±132.31	481.79±405.66	280.20±130.27
Bladder	1346.92±125.12	2992.46±1655.24	925.58±798.48	14.32±6.24
Testes	77.75±6.60	75.18±8.79	38.56±7.01	4.15±1.01
Prostate	249.14±36.02	124.03±37.13	63.47±30.56	9.66±5.24
Skin	244.46±22.30	172.82±7.16	67.29±10.52	10.06±3.00
Blood	711.89±49.62	299.27±22.53	106.46±7.25	17.25±1.14
Plasma	1432.49±88.53	623.18±7.12	180.82±18.25	17.00±0.64

Tissue	Mean (±SD) TBX Concentrations (ng eq/g)			
	10 min	1 hr	3 hr	24 hr
PREGNANT ♀ (GD18)				
Adrenal	427.61±65.12	212.42±39.33	170.20±54.40	14.85±5.67
Bladder	261.90±88.04	412.96±134.77	367.12±109.26	21.09±10.89
Blood	463.16±28.25	285.41±50.15	143.77±6.56	25.62±5.08
Bone Marrow	229.29±40.95	137.28±21.23	125.03±34.85	28.77±18.84
Cecum	508.91±376.53	347.62±126.50	1696.16±233.19	485.21±110.93
Cerebellum	44.38±1.41	27.34±2.68	18.97±2.94	5.46±1.03
Cerebrum	42.48±3.25	27.95±3.66	18.15±3.64	5.47±1.37
Eye Ball	65.51±4.32	63.07±10.57	29.14±12.18	7.59±2.19
Fat	69.91±4.86	91.12±43.42	80.54±38.05	6.48±1.11
Heart	300.08±56.43	145.05±29.58	78.75±16.42	8.60±3.09
Kidney	7375.93±773.77	6606.69±513.77	3602.53±1107.08	114.25±25.56
Large Intestine	191.72±107.99	219.06±85.26	329.28±85.45	637.47±208.53
Liver	1383.38±100.58	887.92±53.43	265.98±35.16	16.90±6.37
Lung	437.09±21.91	255.51±66.06	162.66±35.20	12.05±1.74
Muscle	129.77±8.47	73.73±10.50	43.53±9.47	5.32±1.36
Ovary	299.78±31.60	155.81±48.70	105.57±28.63	9.92±3.10
Pancreas	593.39±197.76	273.89±62.60	113.16±29.08	13.30±6.00
Pituitary	221.09±54.98	144.15±11.07	103.31±9.23	32.88±2.34
Plasma	938.06±63.90	413.92±97.56	220.91±9.76	30.69±9.85
Skin	196.51±15.81	187.26±22.44	113.94±39.86	10.15±2.58
Small Intestine	1165.61±184.06	1396.33±296.35	5134.85±632.61	69.79±17.91
Spleen	255.05±50.10	156.23±42.81	68.02±24.55	7.56±2.77
Stomach	30688.27±3772.19	25104.21±6737.24	17766.04±870.55	43.30±20.04
Thymus	225.77±45.60	132.41±34.62	80.35±24.08	8.61±2.08
Thyroid	271.46±63.54	226.61±21.93	146.67±15.17	68.67±9.01
Trachea	533.98±247.91	151.25±4.48	102.85±35.64	18.00±4.06
Uterus	214.49±12.39	176.99±25.09	120.08±32.82	10.88±3.73
Placenta	152.86±1.64	156.19±37.57	95.50±19.93	11.87±2.82
Amniotic Fluid	2.27±0.13	53.66±2.89	21.44±3.81	17.30±4.93
Fetus	74.75±16.38	84.91±15.59	49.23±14.89	10.74±2.61
Fetus Blood	89.09±2.86	116.71±21.43	64.05±15.02	18.59±3.57
Fetus Brain	34.75±2.36	36.96±3.99	24.90±1.53	6.67±1.18
Fetus Heart	80.62±4.29	91.66±14.55	56.16±10.03	17.63±2.20
Fetus Lung	66.99±10.13	75.40±10.05	45.11±9.71	8.44±1.91
Fetus Liver	45.11±5.40	60.75±23.22	29.12±7.68	7.35±1.85
Fetus Kidney	108.01±5.92	96.19±26.18	57.62±8.57	16.06±6.60

- Milk Transfer - Data showed that the radioactivity in the milk at 3 h after dosing was higher than that in the maternal blood. Relative concentrations of radioactivity in maternal blood and ingested milk in suckling rats at various time points after oral administration of ^{14}C-TBX to lactating rats (n=3) are listed in the following tables.

	TBX Concentrations (ng eq/ml)			
	1 hr	3 hr	6 hr	24 hr
Ingested Milk	20.49±26.66	251.13±59.23	123.24±19.26	40.46±7.66
Maternal Blood	131.16±6.73	92.51±13.56	85.62±6.68	10.70±4.16

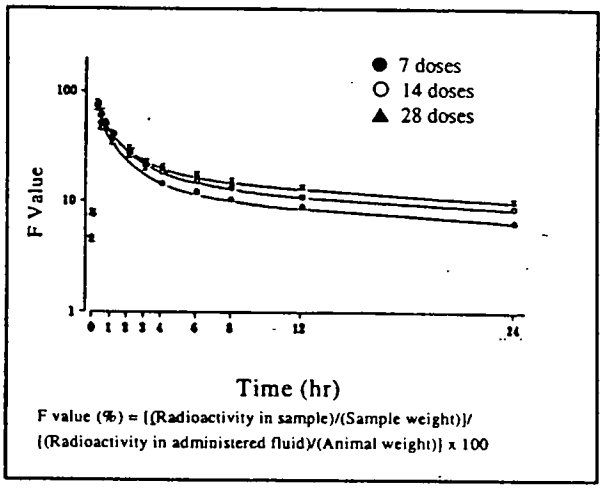
2.2.1.2. Studies on the Metabolic Fate of TBX (2): Absorption, Distribution and Excretion in Rats After Daily Oral Administration of ^{14}C-TBX. Jpn Pharmacol Ther. 1989; 17(4): 1231-1239. (89005)(Vol. 13.1, p 1)

Compound: [^{14}C]-TBX, 46.5 mCi/mmol.
Dose/Route: 1 mg/5 ml/kg iv or po
Dosing Duration: 28 days
Animals:

- ♂ SD rats, 8 weeks old;
- pregnant ♀ rats (GD 18); and
- dams with pups at Post Partum Day 10.

Results:

- Radioactivity in the Blood - Relative concentrations (expressed as F values) of radioactivity in blood (n=3) after 7-, 14-, and 28-day of repeated dosing were depicted in the right figure. Accumulation did occur as higher relative exposures (F values) were noted after 14 and 28 repeated doses.



- Excretion Rates in Urine and Feces - The ratio of radioactivity excreted through urine and feces was 2:1 following either single or repeated doing. The cumulative excretion of radioactivity through urine and feces was 98-99%.
- Whole Body Autoradiography - Autoradiographs revealed that high levels of radioactivity were observed in the stomach and small intestine contents at 10 min after dosing. In addition, strong radioactivity signals were identified in the kidney, bladder, liver, lung, blood and trachea.
- Tissue Distribution of Radioactivity - A slight increase of the radioactivity concentrations was observed in the organs and tissues with increasing number of doses. The following table shows summarized data of the tissue distribution of radioactivity in ♂ rats (n=3) at 24 hours after 7, 14, and 28 days of repeated oral dosing.

Tissue	Mean (±SD) TBX Concentrations (ng eq/g)			
	24 hr Post 7 Doses	24 hr Post 14 Doses	24 hr Post 28 Doses	7 Days Post 28 Doses
Cerebrum	10.22±0.81	16.53±3.21	16.25±1.19	9.73±1.72
Cerebellum	10.18±1.06	19.12±2.88	19.64±0.73	9.37±1.25
Pituitary	49.29±9.18	61.14±21.11	75.03±48.23	49.42±23.32
Eye Ball	11.33±1.87	16.03±1.10	14.97±1.19	10.84±1.32
Thyroid	230.06±26.52	246.78±39.99	318.94±66.92	212.02±31.47
Thymus	19.89±2.65	37.50±2.38	38.02±2.84	19.49±2.69
Heart	14.50±2.37	22.49±1.71	22.97±3.81	14.71±1.26
Lung	18.57±0.80	32.54±7.78	38.62±9.03	17.17±0.51
Trachea	57.59±3.64	92.77±9.99	90.79±5.30	59.76±7.32
Liver	51.67±3.89	71.39±0.96	69.93±1.19	50.31±8.10
Spleen	22.49±2.56	40.74±1.85	40.74±2.54	21.50±1.59
Pancreas	43.35±4.99	69.99±3.37	70.45±2.77	38.03±0.62
Kidney	38.37±5.83	67.85±2.40	63.73±3.53	34.00±5.03
Adrenal	48.38±4.91	69.09±15.58	57.13±4.41	52.89±5.21
Fat	17.47±5.28	34.53±1.74	34.49±2.28	13.51±1.95
Muscle	9.06±0.92	16.76±6.05	17.90±5.71	7.61±0.39
Bone Marrow	44.78±2.99	128.87±9.15	123.68±13.13	35.51±7.13
Stomach	62.94±41.33	106.78±33.58	79.91±28.43	2.84±0.33
Small Intestine	127.41±47.32	143.84±76.89	143.18±23.14	4.15±0.56
Cecum	288.19±65.78	292.89±83.57	321.56±43.60	3.39±0.90
Large Intestine	450.45±120.41	457.73±53.62	420.68±54.87	3.14±0.38
Bladder	38.29±6.24	75.55±8.30	83.77±9.30	37.41±9.24
Testis	15.78±2.12	27.83±3.34	28.99±2.17	13.66±0.65
Prostate	23.48±2.08	31.13±4.96	26.19±1.13	22.30±1.67
Skin	32.79±2.84	48.97±2.80	51.36±1.36	31.17±1.86
Blood	65.34±1.99	86.61±1.56	100.01±4.39	49.82±1.79
Plasma	49.35±2.14	49.62±2.43	40.97±2.15	20.85±1.89

2.2.1.3. Plasma Concentration of Pemirolast Potassium (TBX) with the Repeated po Administration at the Toxic Dose. Toxicol Sci. 1996; 21: 401. (96001)(Vol. 1.13, p 30)

Note: The following information was summarized by the reviewer based on a submitted abstract in the current NDA.

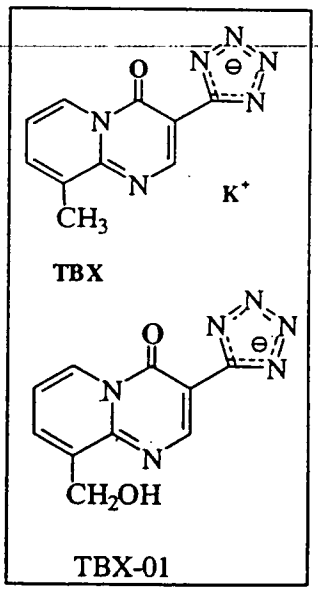
Compound: Pemirolast Potassium (TBX)
Dose & Route: 50 mg/kg po
Dosing Duration: 4 weeks
Animal: ♂ Crj:CD Rats, 5 weeks of age.
Blood Collection: Day 1 and Weeks 1 and 4 at 0.5, 1, 2, 3, 4, 8, and 24 hr post dosing.

Results: Data of mean plasma levels of various time points showed two peak values. Summarized mean PK parameters for TBX following single and repeated oral dosing are presented in the following table. Higher plasma AUC and C_{max} values were obtained during Weeks 1 and 4, an indicative of accumulation of TBX following repeated oral dosing.

Parameters	Single Dose		Week 1		Week 4	
T_{max} (hr)	1	4	2	8	2	8
C_{max} (μg/ml)	1.8	4.4	19.4	16.4	22.9	40.4
$AUC_{0\text{-}24}$ (μg•hr/ml)	76.8		246.9		499.6	

2.2.1.4. Urinary Excretion of TBX administered in High Doses to Rats. (SR2317)(Vol. 1.13, p 31)

Report Nº: SR2317
Study Nº: 6K090, KAUL-S-21696
Compound: Pemirolast Potassium dissolved in distilled H_2O
Dose & Route: 50 and 250 mg/kg, 5 ml/kg po for 1 day or 29 days
Animal: ♂ & ♀ SD Rats, 6 weeks of age
Compliance with GLP/QAU: Not indicated.
Test Period: 11/9/1988 - 3/31/1989
Study Designs: Rats were maintained in a metabolic cage immediately after oral administration of TBX, 50 or 250 mg/kg. Urine samples were collected 24, 48, and 96 post dosing and urine TBX and calcium salt of the main metabolite of TBX [TBX-01, 1-hydroxymethyl-3-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-a]pyrimidin-4-one] concentrations were assayed by an HPLC method. The urine samples collected at 6 hr after 1-, 4-, 7-, 14-, 21-, 29-day repeated dosing of TBX (250 mg/kg) were examined microscopically for the urine crystals. Bladder contents were also evaluated macro- and microscopically 24 hr after the last dose.



Results:

- Urinary Excretion Following a Single Dose Administration - Cumulative urine excretion of TBX and TBX-01 in the rat after a single oral dose are presented in the following table.

Dose (mg/kg)	Urinary Metabolites	Cumulative Urinary Excretion (% of Dose)					
		0-24 hr		0-48 hr		0-96 hr	
		♂	♀	♂	♀	♂	♀
50	TBX	2.4 ± 0.9	4.5 ± 1.3	2.6 ± 1.0	4.9 ± 1.3	2.7 ± 1.0	5.0 ± 1.3
	TBX-01	28.8 ± 2.1	32.3 ± 0.8	29.8 ± 2.0	33.5 ± 1.0	30.0 ± 2.0	33.8 ± 1.1
250	TBX	1.3 ± 0.1	1.6 ± 0.3	1.5 ± 0.2	1.8 ± 0.3	1.6 ± 0.2	1.9 ± 0.3
	TBX-01	30.3 ± 2.5	30.7 ± 0.6	33.0 ± 1.1	33.7 ± 0.9	33.4 ± 1.0	34.3 ± 0.9

- Urinary Excretion Following Repeated Oral Dose Administration - The levels of TBX-01 in male and female rats after 28-day repeated oral doses of 250 mg/kg are as follows.

Sex	Urinary Levels of TBX-01 (μg/ml, N=4)				
	0-2 hr	2-4 hr	4-6 hr	6-8 hr	8-24 hr
♂	1388 ± 764	1604 ± 408	785 ± 148	839 ± 73	831 ± 54
♀	1513 ± 131	1325 ± 152	1127 ± 181	1641 ± 431	835 ± 285

Urinary excretion of TBX and TBX-01 in ♂ and ♀ rats after repeated oral administration for 29 days are shown in the following table.

Dose (mg/kg)		Urinary Metabolites	Cumulative Urinary Excretion (% of Dose) in 24 hr					
			Day 1	Day 4	Day 7	Day 14	Day 21	Day 29
50	♂	TBX	1.8 ± 0.5	1.0 ± 0.1	1.4 ± 0.1	2.0 ± 0.4	2.0 ± 0.8	2.4 ± 0.5
		TBX-01	35.5 ± 1.0	35.9 ± 1.0	40.2 ± 1.1	38.0 ± 1.1	38.9 ± 1.4	35.5 ± 1.0
	♀	TBX	4.1 ± 0.8	2.1 ± 0.5	2.5 ± 0.5	3.1 ± 0.8	3.7 ± 0.5	4.4 ± 0.9
		TBX-01	37.8 ± 0.7	39.4 ± 0.3	41.1 ± 0.7	39.9 ± 0.9	39.6 ± 0.2	40.3 ± 0.9
250	♂	TBX	1.1 ± 0.1	1.0 ± 0.2	1.6 ± 0.5	1.3 ± 0.2	1.4 ± 0.1	1.4 ± 0.1
		TBX-01	37.5 ± 1.9	35.5 ± 5.0	36.1 ± 4.1	34.6 ± 2.5	36.7 ± 2.1	38.8 ± 1.7
	♀	TBX	2.2 ± 0.2	1.5 ± 0.4	1.6 ± 0.4	1.6 ± 0.4	2.0 ± 0.8	2.1 ± 0.3
		TBX-01	35.0 ± 2.8	38.3 ± 2.5	36.6 ± 3.5	40.4 ± 1.8	38.5 ± 1.9	36.5 ± 3.1

- Examination of Urine Crystals - The crystals formed from the TBX metabolite could be detected in urine of male rats after the first administration of the drug at a dose of 250 mg/kg. In contrast, crystals were not formed until after 7-day dosing in the female rats. The following table shows the presence of urine crystals and urine TBX-01 concentrations following oral administration of 250 mg/kg TBX to rats on Days 1, 4, 7, 14, 21, and 29. No bladder stones were detected.

Animal Nº	Day 1		Day 4		Day 7		Day 14		Day 21		Day 29	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	- (1131)	- (586)	- (539)	- (1151)	- (615)	+ (660)	- (603)	+ (1204)	+ (732)	++ (1372)	+ (1496)	++ (2172)
2	+ (832)	- (973)	+ (739)	- (1028)	+ (774)	- (776)	++ (1178)	+ (492)	++ (1100)	- (453)	++ (914)	- (559)
3	- (836)	- (424)	- (604)	- (305)	- (822)	- (519)	- (934)	- (994)	- (1276)	- (248)	- (1095)	+ (1785)
4	- (700)	- (512)	- (616)	- (623)	- (738)	- (985)	- (746)	+ (1958)	+ (811)	+ (1013)	++ (1059)	- (789)

- not observed, + slight, ++ remarkable; Values in parentheses denote urinary TBX-01 levels (μg/ml).

2.2.1.5. Plasma Level and Urine Excretion in Dogs After Administration of TBX. Jpn Pharmacol Ther 1990; 18(3). (90004)(Vol. 1.13, p 135)

Compound: Pemirolast Potassium

Dose/Route: 0.2, 1, and 5 mg/ml/kg in H_2O for po; 0.2 and 1.0 mg/ml/kg in saline iv

Animal: ♀ Beagle dogs

Study Designs: This was a cross over study with one week washout period between iv and oral administration. For the food effect study, the animals were given food 1 hr prior to oral administration of 0.2 mg/kg TBX.

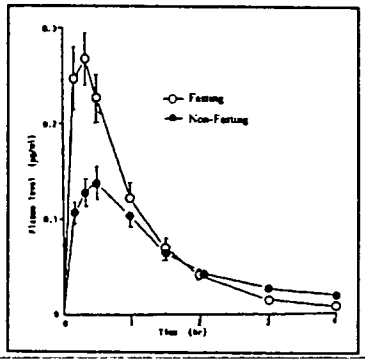
Results:

- Plasma TBX PK Parameters - The PK parameters in the plasma for TBX following iv and oral administration are presented as followings.

Parameters	Dose (mg/kg)- IV		Dose (mg/kg)- Oral		
	0.2	1	0.2	1.0	5.0
K_e (hr^{-1})	1.078 ± 0.071	1.044 ± 0.087	6.197 ± 1.131	3.965 ± 0.561	0.943 ± 0.181
K_e (hr^{-1})	-	-	0.984 ± 0.065	0.932 ± 0.098	0.667 ± 0.035
$T_{1/2}$ (hr)	0.668 ± 0.048	0.710 ± 0.071	0.732 ± 0.052	0.894 ± 0.193	1.064 ± 0.057
T_{max} (hr)	-	-	0.315 ± 0.043	0.555 ± 0.088	1.722 ± 0.313
C_{max} (μg/ml)	-	-	0.235 ± 0.015	0.996 ± 0.112	4.359 ± 0.564
V_d (L/kg)	6.191 ± 0.367	5.312 ± 0.284	-	-	-
CL (ml/min)	107.8 ± 9.4	91.3 ± 9.7			
AUC (μg•hr/ml)	0.416 ± 0.026	2.567 ± 0.251	0.307 ± 0.027	1.737 ± 0.182	15.895 ± 1.563
Absolute BA (%)	-	-	75.5 ± 3.6	66.6 ± 4.6	-

Values expressed as mean ± SE (n=9).

Data showed that food reduced and delayed drug absorption from the GI resulting in lower C_{max} and AUC values as depicted in the right figure. The food effect on plasma PK parameters for TBX following a single oral dose of 0.2 mg/kg to dogs is tabulated in the following table.



Parameters	Fasting	Non-Fasting
C_{max} (μg/ml)	0.283±0.020	0.137±0.019*
T_{max} (hr)	0.267±0.041	0.433±0.067
AUC (μg•hr/ml)	0.315±0.037	0.270±0.014

Values are the mean ± SE (n=5); *p<0.05.

- Urine Excretion of TBX - Following oral administration of 0.2 mg/kg of TBX, ~3.9 and 5.1% of the dose excreted from urine during a 24 hr and 48 hr collection, respectively.

2.3. METABOLISM

2.3.1. *METABOLIC PROFILES*

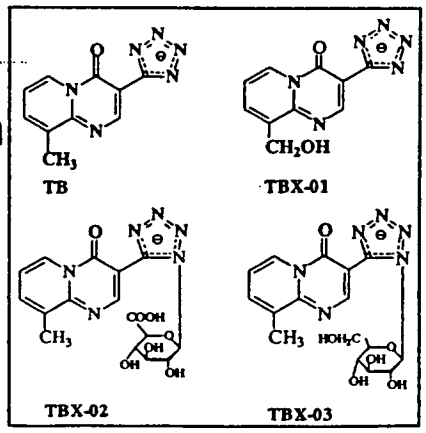
APPEARS THIS WAY
ON ORIGINAL

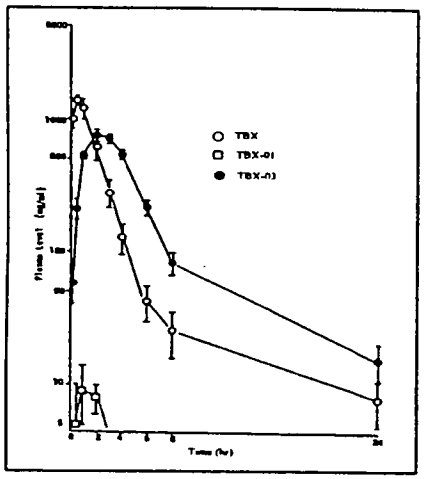
2.3.1.1. Identification and Determination of Metabolites in Dog's Urine After Administration of TBX. Jpn Pharmacol Ther 1990; 18(3). (90005)(Vol. 1.13, p 153)

Compound: Pemirolast Potassium
Dose: 50 mg/kg in capsule po or 1 mg/4 ml/kg by gavage
Animal: ♂ and ♀ beagle dogs, weighing 13-15 kg
Method of Analysis: [redacted]
Study Designs: Dogs were given TBX 50 mg/kg in capsules. Blood was collected various time points and urine was sampled at 0-3, 3-6, 6-24, and 24-48 hr post doing.

Results:

- Metabolic Profiles of TBX in Dog Plasma [redacted] of urine showed 4 peaks that represented unchanged TB, TBX-03, a glucoside of TBX, TBX-01, a hydroxyl metabolite, and TBX-02. The molecular structures of these metabolites are illustrated in the right figure. The following figure depicts the kinetics of mean plasma levels of unchanged parent compound and metabolites following oral administration of 1 mg/kg TBX.





- Metabolic profiles of TBX in Dog Urine [redacted] of urine showed three [redacted] that represented unchanged TB, TBX-03, a glucoside of TBX, and TBX-01, a hydroxyl metabolite. The molecular structures of these metabolites are illustrated in the above right figure. Accumulative urinary excretions of TBX following oral administration of 1 mg/kg were 19.3%, 48.4%, 64.8%, and 67% of dose 3, 6, 24 and 48 hr, respectively. The major metabolite excreted in the urine was TBX-03, which represented 62.8% of dose eliminated within 48 hr post dosing. Contrarily, only small amounts of unchanged drug and TBX-01, the hydroxyl metabolite, were present in the urine excretion with values of 2.9 and 1.7% of dose, respectively.

2.3.2. *Effects on Hepatic Enzymes*

2.3.2.1. Effects of TBX on Drug-Metabolizing Enzymes. (SR2318)(Vol. 1.13, p 113)

Report Nº: SR2318
Compound: Pemirolast Potassium (Lot Nº 18) in H_2O
Dose: 10, 50, and 250 mg/kg po for 30 days
Control: H_2O
Animal: ♂ & ♀ Crj:CD (SD) rats, 5-week-old, weighing 203-242 g for ♂ and 138-178 g for ♀
Compliance with GLP/QAU: Not indicated.
Test Period: 6/11/1984 - 1/28/1984

Results: Significant increases in absolute (♂: ↑15%; ♀: ↑19%) and relative (♂: ↑21%; ♀: ↑39%) liver weights were noted in rats at 250 mg/kg. TBX, administrated orally for 30 days, had little or no effects on cytochrome p-450 content and NADPH-cytochrome C reductase activity. A slight increase in cytochrome b_5 content (↑13%) and a significant decrease in the NADPH-cytochrome b_5 reductase activity (↓19%) were seen in the ♂ and ♀ at 250 mg/kg, respectively. Slight increases in the aminopyrine N-demethylase (♂: ↑38%; ♀: ↑48%) and aniline hydroxylase activity (♂: ↑36%; ♀: ↑27%) were found in rats at 250 mg/kg. Male rats at 50 mg/kg also had an elevated aniline hydroxylase activity by 25%. TBX had no effect on the hexobarbital-induced sleeping time in both ♂ & ♀ rats; yet a slight reduction (↓19%) in the cerebral hexobarbital concentration was detected in the ♂ rats at 10 mg/kg.

2.4. Plasma Protein Binding

2.4.1.1. Plasma Protein Binding Study of TBX *In Vitro*. (SR2319)(Vol. 1.13, p 179)

Plasma Binding of TBX *In Vitro*. Jpn Pharmacol Ther 1990; 18 (3): 1049-1050. (SR2319-P)(Vol. 1.13, p 189).

Report Nº: SR2319 & SR2319-P
Study Nº: 88-816, KAUL-S-21181
Study Aims: To determine *in vitro* plasma protein binding of TBX with samples from rats, dogs, and humans.

Compound: Pemirolast Potassium
Compliance with GLP/QAU: Not indicated.
Study Sites: [redacted]

Testing Period: 8/4/1988 - 9/12/1988
Plasma Source: rat (♂ Jcl:SD), dog (♂ beagles) and human (♂ healthy volunteers)

Results: The *in vitro* binding of TBX to rat, dog, and human plasma, and human serum albumin (HSA) are as listed in the following table. The binding of TBX to the serum protein varied from species to species. The highest binding affinity was seen with human plasma and HSA. Similar binding affinity was noted for human plasma and HSA.

TBX (μg/ml)	Ratio of Binding (%)*			
	Rat Plasma	Dog Plasma	Human Plasma	HSA
0.1	84.1 ± 0.2	64.5 ± 0.7	95.6 ± 0.2	ND
0.5	85.3 ± 0.2	67.3 ± 0.8	95.6 ± 0.1	96.1 ± 1.4
2.5	84.0 ± 0.2	66.2 ± 1.0	95.6 ± 0.2	96.9 ± 0.2

* Data were expressed as the mean ± SD of 3 experiments.

3. TOXICOLOGY

3.1. OCULAR TOXICITY

3.1.1.1. Ocular Irritation Test of Pemirolast Potassium Ophthalmic Solution (TBX) in Rabbits. (SR2012)(Vol. 1.13, p 199)

Report Nº: SR2012
Study Nº: SRT-402, 879415
Study Aims: To determine ocular irritation of TBX in the rabbit by a single day frequent instillation.
Compound: Pemirolast Potassium (Lot Nº M-10): 0.1 (Lot Nº TBX871005-3), 0.5 (Lot Nº TBX871005-2) and 1.0% (Lot Nº TBX871005-1)
Dose: 10 instillations/day, 1 drop each instillation, at 30-min intervals
Vehicle Control: **The compositions of vehicle control were not stated in the submission.**
Negative Control: Physiological Saline
Animal: Japanese male albino rabbits, weighing 2.0-3.0 kg, 5/group
Study Site: Santen Pharmaceutical Co., Ltd., 9-19, Shimoshinjo 3-chome, Higashiyodogawa-ku, Osaka, 533, Japan
Compliance with GLP/QAU: Yes (Japanese)
Study Date: 10/1987 - 21/1987
Dosing Date: 10/9/1087

Study Designs: Saline, vehicle control, or test TBX solution (0.1, 0.5 or 1.0%) was instilled into the left conjunctival sac of each rabbit. Ocular irritation, aqueous flare, blinking frequency, and corneal epithelial lesions were assessed.

Results: Slight palpebral conjunctival congestion was observed in both treated and non-treated eyes in all groups. There was no significant difference among groups. One animal in each of 0.1 and 0.5% TBX groups had signs of congestion in nictitating membranes. No abnormalities were noted in corneas or anterior chambers. The score of corneal epithelial lesions in each group was similar. The mean blinking frequency was 0.2-1.8 times/min for each group. Therefore, 0.1, 0.5 or 1.0% TBX and its vehicle did not cause any eye irritation or damage during one day frequent instillation in rabbits.

3.1.1.2. Single Day/Frequent Instillation Schedule with Aged TBX. (SR2015)(Vol. 1.13, p 212)

Report Nº: SR2015
Study Nº: SRT 405, 889414
Study Aims: To determine ocular irritation of aged 0.1% TBX, which was stored at 40°C in 75% relative humidity for 6-mon, in rabbits by a single day frequent instillation.
Compound: Pemirolast Potassium (Lot Nº M-10): 0.1% (Lot Nº TBX880125-2), stored at 40°C for 6 mon; 0.1% TBX (Lot Nº TBX881209-2), freshly prepared
Dose: 10 instillations/day, 1 drop each instillation, at 30-min intervals
Vehicle Control: **The compositions of vehicle control were not stated in the submission.**
Animal: Japanese male albino rabbits, weighing 2.28-2.73 kg, 7/group
Study Site: Santen Pharmaceutical Co., Ltd., 9-19, Shimoshinjo 3-chome, Higashiyodogawa-ku, Osaka, 533, Japan
Compliance with GLP/QAU: Yes (Japanese)
Study Date: 12/1988 -1/1989
Dosing Date: 12/28/1988

Methods: Vehicle control, or test 0.1% TBX solution (aged or freshly prepared) was instilled into the left conjunctival sac of each rabbit. Ocular irritation, aqueous flare, blinking frequency, and corneal epithelial lesions were assessed.

Results: A slight congestion of the palpebral conjunctiva was observed in treated eyes of each group. There was no significant difference among the groups. No abnormality was seen in any cornea or anterior chamber. The mean blinking frequency and scores of corneal epithelial lesions were similar in each group. Therefore, the results suggested that one day frequent instillation of aged TBX ophthalmic solution do not cause ocular irritation.

3.1.1.3. Single Day/Frequent Instillation Schedule with Light Exposed TBX. (SR2016)(Vol. 1.13, p 226)

Report Nº: SR2016
Study Nº: 939410
Study Aims: To determine ocular irritation of TBX that had exposed to severe light conditions in rabbits by a single day frequent instillation.
Compound: Pemirolast Potassium (Lot Nº BF06): 0.1% (Lot Nº PT50130), pH 7.9, exposed to light at 600000 lux•Hr; 0.1% TBX (Lot NºPT50130), freshly prepared
Dose: 10 instillations/day, 1 drop each instillation, at 30-min intervals
Vehicle Control: **The compositions of vehicle control were not stated in the submission.**
Animal: Japanese male albino rabbits, weighing 2.04-2.34 kg, 6/group
Study Date: 6/15/1993 - 8/26/1993
Dosing Date: 7/16/1993
Study Site: Santen Pharmaceutical Co., Ltd., 9-19, Shimoshinjo 3-chome, Higashiyodogawa-ku, Osaka, 533, Japan
Compliance with GLP/QAU: Yes (Japanese)
Methods: Vehicle control or test 0.1% TBX solution (light-exposed or freshly prepared) was instilled into the left conjunctival sac of each rabbit. Ocular irritation, aqueous flare, blinking frequency, and corneal epithelial lesions were assessed.

Results: No significant findings were noted for all the examined parameters. Therefore, the results implied that one day frequent instillations of light-exposed 0.1% TBX ophthalmic solution do not cause ocular irritation.

3.1.1.4. Ocular Irritation Test of Pemirolast Potassium Ophthalmic Solution (TBX) in Rabbits for one month. (SR2013)(Vol. 1.13, p 241)

Report Nº: SR2013
Study Nº: SRT-403, 879418
Study Aims: To determine the potential of TBX, to induce ocular irritation in rabbits following 28-day ocular application.
Compound: Pemirolast Potassium (Lot Nº M-10): 0.1 (Lot Nº TBX871116-2), 0.5 (Lot Nº TBX871116-3) and 1.0% (Lot Nº TBX871117 and TBX871130)
Dose: 4 instillations/day for 28 days, 1 drop each instillation, at 2-hr intervals.
Dosing Duration: 28 days.
Vehicle Control: **The compositions of vehicle control were not stated in the submission.**
Animal: Japanese male albino rabbits, weighing 2.0-3.0 kg, 10/group
Study Date: 11/1987 - 3/1988
Compliance with GLP/QAU: Yes (Japanese)

Study Site: Santen Pharmaceutical Co., Ltd., 9-19, Shimoshinjo 3-chome, Higashiyodogawa-ku, Osaka, 533, Japan

Study Designs: Vehicle control or test TBX solution (0.1, 0.5 or 1.0%) was instilled into the left conjunctival sac of each rabbit 4x/day for 28 days. Animals were observed daily for the general condition. Ocular irritation and weight measurement were recorded on Days 7, 14, 21 and 27. The aqueous flare was assessed on Days 0, 7, and 14. Corneal epithelial lesions were examined on Day 27. Lenses were checked on Days 0 and 28. The fundus was observed and photographed on Day 28. Animals were sacrificed on Day 28 after the final instillation and histopathological examination was performed.

Results:

- General Condition, Food Consumption & Weight Gain - No treatment-related changes were noted.
- Ocular Irritation - Slight congestion in the palpebral conjunctiva or the nictitating membrane was observed in treated eyes in all groups; no significant difference among groups was noted.
- Aqueous Flare - No abnormalities in the cornea or anterior chamber were seen.
- Corneal Epithelial Lesions - No treatment-related lesions were noticed.
- Histopathological Examination - The sponsor stated that no histopathological abnormalities developed in the eyeballs or their appendages in any examined eyes. **However, no detailed pathological data were submitted.**

3.1.1.5. Three Months Ocular Toxicity Study of TBX Eye Drops (DE-068) in Rabbits. (SR2322)(Vol. 1.14, p 001)

Toxicological Study of TBX Eye Drops (DE-068) in Rabbits: Ocular Irritation Test and Systemic Influence with Topical Application for Three Months. The Clinical Report. 1990; 24:2659-2668. (SR2322-P)(Vol. 1.14, p 77)

Report Nº: SR2322 & SR2014
Study Nº: SRT-404, 5068
Study Aims: To determine the potential of TBX to induce ocular irritation in rabbits following 91-day ocular application.
Compound: Pemirolast Potassium (Lot Nº M-10): 0.1% (Lot Nº TBX881222-2), pH 8.15
Dose: 1 drop every 2 hr, 4 instillations/day
Dosing Duration: 91-day
Vehicle Control: **The compositions of vehicle control were not stated in the submission.**
Animal: Japanese male albino rabbits, weighing 2.28-2.76 kg, 10/group
Compliance with GLP/QAU: Yes (Japanese)
Study Site:
Study Date: 12/20/1988 - 11/10/1989
Dosing Date: 1/25/1989 - 4/25/1989

Study Designs: Vehicle control or test TBX solution (0.1%) was instilled into the left conjunctival sac of each rabbit 4x/day for 91 days. The following observations were performed.

- General Sings and Mortality - 1x/day.
- Food Intake -1x/day.
- Body Weight - 1x/week for Weeks 1-4 and 1x/2 weeks thereafter.
- Clinical Pathology - Urinalysis, Week 13; Hematology and Blood Chemistry, Day 91. The following table shows the parameters analyzed during clinical laboratory evaluations.

HEMATOLOGY	SERUM CHEMISTRY		URINALYSIS
RBC	ALT	Inorganic Phosphorus	Appearance pH
WBC with Differential	Albumin	Total Bilirubin	Bilirubin
Ht	A/G Ratio	Total Cholesterol	Protein
Hb	ALP (Alkaline Phosphatase)	Glucose	Glucose
MCV	Lactate Dehydrogenase (LDH)	Creatinine	Specific Gravity
MCHC	AST	Total Protein	Ketones
MCH	Sodium	γ-Glutamyltransferase	Urobilinogen
Platelet Count	Potassium	Triglycerides	Occult Blood
Reticulocyte Count	Calcium	Globulin	Total Volume
PT aPTT	Urea Nitrogen		Microscopic Examination of Sediment

- Ophthalmological Examination (ocular irritation, aqueous flare, corneal epithelial lesions, lens observation and ophthalmoscopy) - Days -2, 30, 60 and 90 or Days -1, 31, and 91.
- Necropsy - Day 91.

  Organ Weight: The following organs were weighed and pair organs except the eyes were weighed together: the eyes, brain, pituitary, submandibular glands, thyroid glands (including the parathyroid glands), thymus, heart, lungs (including the bronchi), liver, spleen, kidneys, adrenal glands and testes.

  Histopathological Examination: The following organs and tissues, as well as weighed organs, were histopathologically examined: the accessory lacrimal glands, parotid glands, thoracic aorta, trachea, tongue, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, pancreas, mesenteric lymph nodes, urinary bladder, lumbar spine (including spinal cord and bone marrow), femurs, femoral medullae, sternum (including bone marrow), back skin, mammary glands, epididymis, seminal vesicle and prostate. All tissues were fixed with 10% neutral buffered formalin fixative, except the eyes, which were fixed with glutaraldehyde formalin.

  Electron Microscopic Examination of the Cornea: The corneas of both eyes from 2 rabbits/group were fixed with 2.5% glutaraldehyde and 1% osmium and processed for both scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Results:

- General Clinical Signs - No remarkable clinical signs were observed.
- Body Weight & Food Consumption - No treatment related changes were noted.
- Hematology, Blood Chemistries and Urinalysis - Normal.
- Ophthalmological Examinations - No ocular irritation was noted in either treated or untreated eyes. Aqueous flare was normal for all animals. Neither abnormal funduscopic findings nor unusual appearances in the lens were observed in all animals. The results expressed as slit lamp score for corneal epithelial lesions are presented as follows.

Group	Nº Animals	Pre-B		Day 30		Day 90[a]	
		L[b]	R[c]	L	R	L	R
Vehicle Control	10	0.10	0.20	0.25	0.30	0.13	0.19
TBX Treated	10	0.30	0.15	0.35	0.35	0.19	0.19

[a] Eight animals were used; [b] Mean Score of treated left eye; [c] Mean score of untreated right eye.

- Pathological Findings - Right testicular and epididymal atrophy were characterized in one TBX treated rabbit. Histopathological examination revealed a slight inflammatory cell infiltration in the conjunctiva of untreated eyes of one rabbit from each group. Chondroidal metaplasia in both treated and untreated eyes was seen in one rabbit receiving TBX. Electron microscopic observation did not show any abnormal changes in corneal epithelial cells or fine structure of the corneal stroma in both groups. Inflammatory cell infiltration in the accessory lacrimal gland was noted in either treated or untreated eyes of TBX treated and vehicle control animals.

Based upon reported information, TBX did not produce adverse systemic toxicity or ocular irritations during 91-day repeated instillation (4 x/day).

3.1.1.6. Six-Month Ocular Toxicity Study of Pemirolast Potassium Ophthalmic Solution in Rabbits. (SR2500)(Vol. 1.14, p 114 - Vol. 1.16)

Report Nº: SR2500
Study Nº: [redacted]6776-102
Study Aims: To evaluate the ocular toxicity potential of pemirolast potassium ophthalmic solution following topical instillation on the cornea of rabbits 4x/day for ≥6 months.
Compound: Pemirolast Potassium (Lot Nº M-10): 0.1% (Lot Nº 6A 9001) and 0.25% (Lot Nº 6B1001), pH 8.0-8.2
Dose and Route: 0, 40, and 100 μg/40 μl/dose, topical ocular instillation at 3-hr intervals
Vehicle Control: **The compositions of vehicle control were not stated.**
Animal: Hra:(NZW)SPF rabbits, weighing 2111-2473 g for ♂ and 2066-2429 g for ♀, 6/sex/group.

Group	Compound	Dose (μg/dose)	Dose Vol.	Dosing Frequency	Dosing Duration	Nº of Animals
1	Vehicle Control	0	40 μl	4x/day	6-month	6/sex
2	TBX 0.1%	40				
3	TBX 0.25%	100				

Compliance with GLP/QAU: Yes
Study Site: [redacted]
Dosing Initiation: 4/15/1997
Terminal Sacrifice: 10/16/1997
Study Designs: Vehicle control or test TBX solution (0.1% and 0.25%) was instilled onto the right cornea surface of each rabbit 4x/day for at least 6 months. On the days (Days 9, 16, 23, 30, 59, 87, 115, 144, and 182) of ophthalmological examination, dosing frequency was reduced to 3x/day. Left eye remained untreated but was handled in the same fashion. The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weights and Food Intake - Pre-R (Day 1) and 1x/week.
- Macroscopic Ocular Examinations - 1x/day.
- Ophthalmoscopic Examinations - Days 9, 16, 23, 30, 59, 87, 115, 144, and 182. Ocular irritation was scored according MacDonal-Shadduck system.
- Clinical Pathology - Days -6, 88, and 184/185. The following parameters were analyzed.

HEMATOLOGY	SERUM CHEMISTRY		URINALYSIS	
RBC	ALT	Inorganic Phosphorus	Appearance	pH
WBC with Differential	Albumin	Total Bilirubin	Bilirubin	
Ht	A/G Ratio	Total Cholesterol	Protein	
Hb	ALP (Alkaline Phosphatase)	Glucose	Glucose	
MCV	Lactate Dehydrogenase (LDH)	Creatinine	Specific Gravity	
MCHC	AST	Total Protein	Ketones	
MCH	Sodium	γ-Glutamyltransferase	Urobilinogen	
Platelet Count	Potassium	Triglycerides	Occult Blood	
Reticulocyte Count	Calcium	Globulin	Total Volume	
PT aPTT	Urea Nitrogen		Microscopic Examination of Sediment	

- TK/PK - Days -5, 14, 91, and 183 at 1 hr following the last treatment of that day. Plasma samples were shipped on dry ice to [redacted]

- Necropsy - Week 27 (Day 184/185). A gross postmortem examination was performed on all unscheduled deaths, animals that were sacrificed in extremis and all surviving animals.
  Organ Weights: The following organs were weighed after careful dissection and trimming of fat and other contiguous tissue:

Adrenals	Heart	Liver (with Gallbladder Drained)	Spleen	Thymus
Brain (Including Brainstem)	Kidneys	Ovaries	Testes with Epididymides	

Tissue Preservation: The following tissues (when present) from each animal were preserved in 10% neutral buffered formalin except eyes and eyelids that were placed in modified Karnovsky's fixative (2% paraformaldehyde/2.5% glutaraldehyde in 0.1 M sodium phosphate buffer).

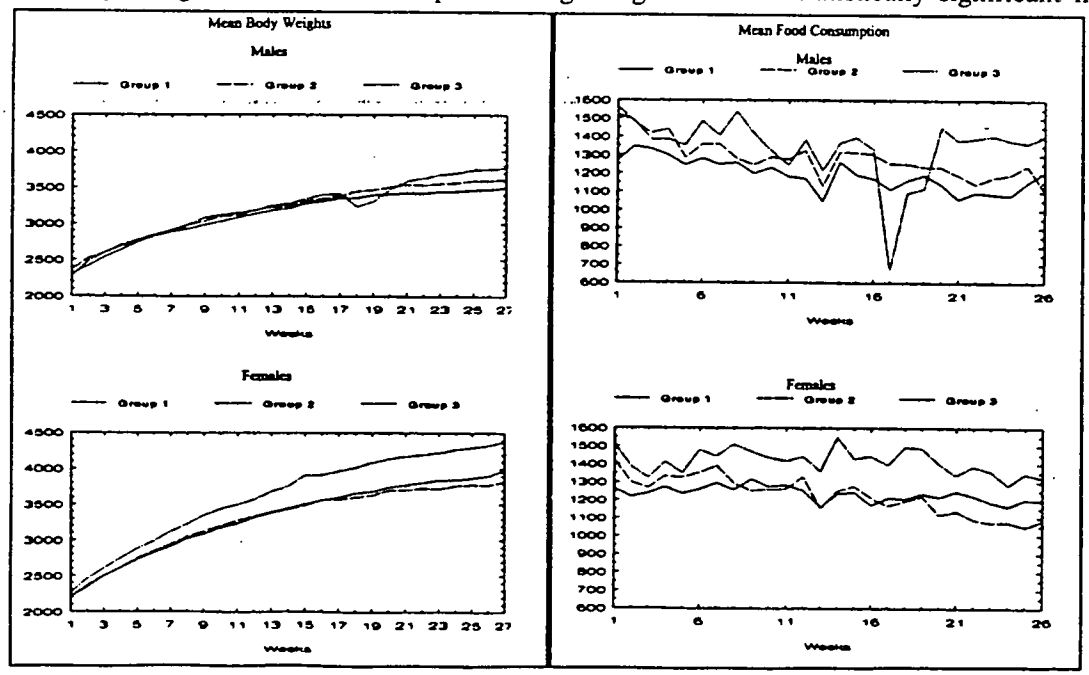
Adrenals	Kidneys (Both)	Eye* (with Optic Nerve) and Eyelids		Spleen	Stomach
Aorta (Thoracic)	Lesions	Pituitary	Pancreas	Skin	Ovaries (Both)
Bone (Femur, Including Knee Joint)		Liver with Gallbladder	Prostate	Testes with Epididymis (Both)	
Bone Marrow (Sternum)	Lung (with Bronchi)	Salivary Glands (Mandibular)	Thymus	Uterus, with Vagina and Cervix	
Brain With Brainstem (Medulla/Pons, Cerebellar Cortex, and Cerebral Cortex)			Spinal Cord (Cervical, Mid-Thoracic, and Lumbar)		
Colon, Cecum, Rectum		Mammary Gland (♀ Only)	Sciatic Nerve	Thyroid (Parathyroids)	
Duodenum, Jejunum, Ileum		Mandibular Lymph Node	Seminal Vesicles	Trachea	
Esophagus	Heart	Mesenteric Lymph Node	Skeletal Muscle	Urinary Bladder	

Histopathology: All eye associated tissues as listed in the following table from control and high-dose animals were examined microscopically.

Palpebral and Bulbar Conjunctiva	Anterior Chamber	Sclera	Retina	Lids
Iris	Posterior Chamber	Ciliary Body		Optic Nerve
Cornea (Including Limbus, Epithelium, Stroma, Descemet's Membrane, and Endothelium)				Lens

Results:

- General Clinical Signs and Mortality - There were 4 unscheduled deaths (1♂ in control at Week 8; 1♂ in Group 2 at Week 17; 3♂ in Group 3 at Weeks 17, 18, and 19, respectively). Cold to touch, hunched posture, pale, hypoactive, diarrhea, poor water intake, and poor appetite were major symptoms observed in the TBX-treated ♂ that died during the study.
- Body Weight & Food Consumption - Slight higher but not statistically significant mean body



weights were noted in high-dose ♀ at Weeks 4→27 (↑5-11%) and ♂ at Weeks 21→27 (↑5-8%). Similarly, high dose animals had higher cumulative body weight changes from Week 1 to Week 26 by 20%. The above two figures depicted mean body weight and food consumption for each group.

- Hematology, Blood Chemistries and Urinalysis - No remarkable changes were attributable to the treatment.
- Ophthalmological Examinations - There were no significant treatment-related changes noted.
- Necropsy -
  Organ Weight: The high dose ♂ had a slight decrease (↓9%) in absolute brain weight.
  Macroscopic Changes - No significant findings were identified in ♂ that die during the study. Enlarged lymph node and ovary cyst were noted in 1 Group 3 ♀.
  Microscopic Findings - Chronic inflammation in the upper and lower eye lids with similar incidence between treated (OD) and untreated (OS) eyes was noted in both control and TBX-treatment animals
- PK/TK - The plasma TBX and it metabolite TBX-01 levels on Days 14, 91, and 183 following ocular administration to rabbits are shown in the following table. Generally, higher concentrations of TBX and TBX-01 were noted on Day 183 than Days 14 or 91 in 0.25% group, an indicative of accumulation.

Group	Day 14		Day 91		Day 183	
	♂	♀	♂	♀	♂	♀
TBX (ng/ml)						
0.1 % TBX	1.399 ± 0.750	1.318 ± 0.156	1.057 ± 0.482	0.733 ± 0.292	0.859 ± 0.397	1.545 ± 0.681
0.25% TBX	1.802 ± 0.508	2.592 ± 1.029	2.348 ± 0.702	2.262 ± 1.251	3.525 ± 2.354	4.732 ± 0.955
TBX-01 (ng/ml)						
0.1 % TBX	0.142 ± 0.156	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
0.25% TBX	0.042 ± 0.102	0.187 ± 0.153	0.116 ± 0.128	0.052 ± 0.127	0.743 ± 1.056	0.883 ± 1.279

3.2. SYSTEMIC TOXICITY

3.2.1. ACUTE TOXICITY

3.2.1.1. BMY-26517 (BLX): Acute Toxicity in Mice. (SR2143)(Vol. 1.17, p 61)

Report Nº: SR2143
Study Nº: 83-003
Study Aims: To determine acute toxicity of TBX in mice following oral and iv administration.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O
Dose & Route: 1030-2745 mg/kg po; 410-800 mg/kg sc, 139-415 mg/kg iv
Animal: Crj:CD-1 (ICR) mice, ~5 weeks of age, weighing 22.0-28.5 g for the ♂ and 18.2-23.5 g for the ♀ in oral administration groups, and 26.1-35.0 g for the ♂ and 20.9-28.5 g for the ♀ in the sc and iv groups; 10/group
Compliance with GLP/QAU: Not Indicated.
Study Site: [redacted]
Study Date: 5/16/1983 - 10/31/1983

Results:

- Mortality & Clinical Signs - General symptoms and mortality were monitored for 7 days after the administration of the drug. Decreased voluntary movement, somnolence and convulsion were the major clinical complaints. Most deaths occurred within 3 hr post dosing. The following table exhibits the LD_{50} of each route of treatment.

Route	LD_{50}	
	♂	♀
PO	1317 (1131.3-1472.2)	1185 (973.4-1325.5)
SC	566 (532.9-602.2)	543 (518.5-567.7)
IV	220 (194.9-247.5)	283 (260.9-308.1)

- Pathology - Gross pathological examination on the dead mice revealed hemorrhaging in the gastric intestinal organs for the oral treatment group, in the subcutaneous area for the subcutaneous treatment group, and in the lungs for the iv group. The characteristics of hemorrhaging was not observed in the survival mice one week post administration.

3.2.1.2. BMY-26517 (BLX): Acute Toxicity in Rats. (SR2142)(Vol. 1.17, p 79)

Report Nº: SR2142
Study Nº: 83-004
Study Aims: To determine acute toxicity of TBX in rats following oral and iv administration.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O
Dose & Route: 500-1790 mg/kg po; 310-620 mg/kg sc, 260-610 mg/kg iv
Animal: Crj:CD-1 (ICR) rats, ~5 weeks of age, weighing 139-171 g for ♂ and 107-136 g for ♀ in oral administration group, and 139-171 g for ♂ and 120-155 g for ♀ in the sc and iv groups; 10/group
Compliance with GLP/QAU: Not Indicated
Study Site:
Study Date: 5/16/1983 - 10/31/1983

Results:

- Mortality & Clinical Signs - General symptoms and mortality were monitored for 7 days after administration of the drug. Somnolence, reduced voluntary movement, salivation, perspiration, tears, erect tail, breathing difficulty and convulsion were the major clinical complaints. Most deaths occurred within 3 hr post dosing. Most survivors showed temporary weight loss. The following table exhibits the LD_{50} for each route of treatment.

Route	LD_{50}	
	♂	♀
PO	755 (649.4-855.7)	687 (535.6-808.1)
SC	430 (408.4-450.0)	474 (449.3-503.8)
IV	372 (343.2-402.8)	389 (359.8-420.2)

- Pathology - Gross pathological examination of the dead rats revealed hemorrhages in stomach and intestines for the oral treatment group, subcutaneous bleeding, hemorrhages in the lung, glandular stomach and intestines, spotty bleeding in the thymus for the subcutaneous treatment group and hemorrhages in the lungs and spotty bleeding in the iv group. The characteristics of hemorrhaging was not observed in the survival rats one week post administration. Precipitation of the drug at the injection sites and GI tract was identified.

3.2.1.3. BMY-26517 (BLX): Acute Toxicity in dogs. (SR2106)(Vol. 1.17, p 98)

Report Nº: SR2106
Study Nº: SBL 85-07
Study Aims: To determine acute toxicity of TBX in dogs following oral administration.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O
Dose & Route: 60, 600, 6000 mg/kg po
Animal: ♂ Beagle dogs, ~6-7 months of age, weighing 7.0-8.8 kg; 2/group

Compliance with GLP/QAU: Yes (Japanese)
Study Date: 7/22/1985 - 10/30/1985
Study Site:

Study Date: 7/22/1985 - 10/30/1985

Results:

- Mortality & Clinical Observations - General symptoms and mortality were monitored at least 2x a day for 2 weeks after the administration of the drug. Vomiting, salivation, tarry stools, loss of appetite, and reddening of the oral mucosa and conjunctiva were major clinical signs. No deaths occurred. The LD_{50} was >6000 mg/kg.
- Food Intake and Body Weights -A decrease in food consumption was noted in one of each at 60 and 6000 mg/kg groups. No significant changes in body weights.
- Pathology - There were no abnormalities in the organ (absolute & relative) weights. Gross pathological examination showed slight red-tinted jejunum mucosa (1 @ 60 mg/kg), slight red-tinted in duodena and ileum (1 @ 600 mg/kg), and hemorrhages in ileum mucosa (1 @ 6000 mg/kg). Thickening of the alveolar septum (1 @ 60 mg/kg), lymphocyte infiltration around bronchi and round cell infiltration in the interstitium in the kidney (1 @ 6000 mg/kg), and leukocyte infiltration in the pancreases and round cell infiltration in the interstitium in the kidney (1 @ 6000 mg/kg) were major lesions seen under microscopic examinations.

3.2.2. SUBACUTE TOXICITY

3.2.2.1. BMY-26517 (TBX): Three-Month Oral Range Finding Study in Mice. (SR2146)(Vol. 1.17, p 182)

Report Nº: SR2146
Study Nº: 6K089
Study Aims: To determine doses for an 18-month carcinogenicity study by given TBX via feed admix to mice for 3 months.
Compound: Pemirolast Potassium (TBX) (Lot Nº M-07) powder
Dose & Route: 0, 1250, 2500, 5000, and 10000 ppm po for 13 weeks with feed mixture
Animal: ♂ & ♀ $B6C3F_1$ mice, ~4-week of age, weighing 19.4-22.2 g for ♂ and 16.2-18.6 g for ♀, 10/sex/group
Compliance with GLP/QAU: Yes
Dosing Initiation Date: 5/22/1986
Necropsy Date: 8/21(♂) -22(♀)/1986
Study Site:

Study Designs: Groups of 10/sex mice were allotted to 5 dose groups as shown in the following table.

Group	Compound	Dose (ppm)	Calculated Dose (mg/kg/day)		Dosing Duration	Nº of Animals
			♂	♀		
1	Control	0	0	0	3 months	10/sex/group
2	TBX	1250	147.3	188.4		
3		2500	305.5	398.1		
4		5000	585.5	664.4		
5		10000				

The following observations were conducted.

- Mortality & Clinical Signs - 1x/day.

- Body Weight & Food Consumption - 1x/week.
- Clinical Pathology (Hematology, Clinical Chemistry and Urinalysis) - Week 13, prior to terminal sacrifice.
- Necropsy - Week 13, all surviving animals. Necropsies were performed immediately on any animals that were found dead.

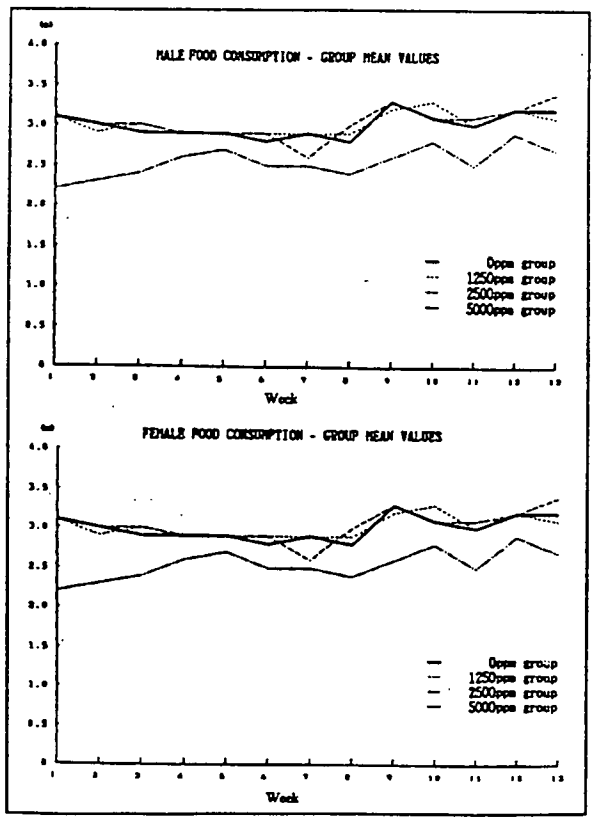
  Organ Weights: Organ weight was recorded for the following organs: liver, kidneys, adrenals, testes, ovaries, brain, heart, lungs, and spleen.

  Tissues/Organs Preserved: The following organs were removed from all the animals, and stored in a 10% neutral buffered formalin solution: brain, pituitary, thyroid-parathyroid, thymus, trachea, lungs, heart, aorta, salivary glands (submaxillary glands, sublingual glands), liver, spleen, adrenals (bilateral), pancreas, testes (bilateral), epididymis (bilateral), prostate, seminal vesicle, ovaries (bilateral), uterus, vagina, skin (ventral), esophagus, stomach (proventriculus, ventriculus), duodenum, jejunum, ileum, cecum, colon, rectum, kidneys (bilateral), urinary bladder, lymph nodes (submandibular and mesenteric), mammary glands (♀ only; abdominal), muscles (femoral; unilateral), sciatic nerve (unilateral), femur (including marrow; unilateral), sternum (including marrow), eyes and accessory glands (bilateral), spine (cervical, thoracic, lumbar), and the lacrimal glands.

  Microscopic Examinations - Sections from the liver, kidneys, urinary bladder, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum of all animals were subjected to microscopic evaluations.

Results:

- Mortality & Clinical Signs - All mice in the 10000 ppm group died with signs of emaciation, hypothermia and crouching within 5-7 days post feeding. No mortality occurred in the other groups.
- Body Weight & Food Consumption - Dose-dependent and statistically significant reductions in mean body weights (♂ - Group 4: ↓12-20%, Weeks 1→13; Group 3: ↓5-9%, Weeks 6→13; Group 2: ↓5-6%, Weeks 9, 11→13; ♀ - Group 4: ↓5-22%, Weeks 1→13; Group 3: ↓5-10%, Weeks 9→13; Group 2: ↓4%, Week 13) and body weight gains were observed in both males and females. Decreased food intake was noticed in the group receiving 5000 ppm as shown in the right figure. No feed efficiency was found in animals receiving ≥2500 ppm. The total mean consumption of test article throughout the treatment in the 1250, 2500, and 5000 ppm groups was 147.3, 305.5, and 585.5 mg/kg/day for the ♂ and 188.4, 398.1, and 664.4 mg/kg for the ♀, respectively.



- Clinical Pathology - An increase in relative neutrophil counts was noted in TBX-treated ♂ (12-17% vs 8%) but not ♀. **However, there were no absolute WBC and differential counts and individual animal**

data provided. LDH (621 vs 492 IU/l) and ALP (209 vs 170 IU/l) values were slightly elevated in ♂ at 5000 ppm. Female mice at 5000 ppm also had increased LDH (1170 vs. 765 IU/l) values. Some TBX-treated males had elevated urine protein (≥300 mg/dl). Rhomboid-shape crystals were found in the urine of animals receiving ≥2500 ppm TBX. An increase in atypical or immature epithelial cells could be identified in the urine of animals at 5000 ppm.

- Gross and Microscopic Pathology -

  Organ weights: Decreased relative and absolute organ weights of testis/kidney of ♂ and ovary/adrenal of ♀ at 5000 ppm were observed.

  Gross Pathology: Macroscopic findings included gonadal atrophy (♂ - seminal vesicle, 9/10; testes, 10/10; ♀ - ovaries, 7/10; uterus 1/10) and calculi in the urinary bladder (4/10♂) in animals at 5000 ppm.

  Histopathology: Microscopic examination found lesions in the following organs.
  - Liver: slight→moderate cytoplasmic vacuolation/necrosis in both ♂ & ♀ @ 10000 ppm.
  - Urinary bladder: slight cytoplasmic vacuolation of mucosal epithelium in 10/10♂ and 10/10♀ @ 5000 ppm; slight→moderate hemorrhage in 10/10♂ and 10/10♀ @ 1250 and 5000 ppm; slight→moderate hyperplasia of mucosal epithelium in 5/10♂ @ 5000 ppm; and slight inflammation of the urinary epithelial mucosa in 8/10 ♂ @ 5000 ppm.

3.2.2.2. BMY-26517 (TBX): Three-month Oral Range Finding Study in Rats. (SR2154)(Vol. 1.19, p 1)

Report Nº: SR2154
Study Nº: 6K087
Study Aims: To determine doses for a 24-month carcinogenicity study by given TBX via feed admix to rats for 3 months.
Compound: Pemirolast Potassium (TBX) (Lot Nº M-08) powder
Dose & Route: 0, 1250, 2500, 5000, and 10000 ppm (~73.7, 149.4, 306.0 and 592.1 mg/kg/day for the ♂ and 72.7, 152.5, 303.3, and 606.8 mg/kg/day for the ♀) po for 13 weeks with feed mixture
Dosing Duration: 13-week
Animal: ♂ & ♀ Fischer rats, ~6-week of age, weighing 84-93 g for the ♂ and 77-86 g for the ♀, 10/sex/group
Compliance with GLP/QAU: Yes
Study Site:
Study Date: 3/10/1986 - 11/28/1986
Dosing Initiation Date: 4/16/1986
Necropsy Date: 7/16(♂)-17(♀)/1986
Study Designs: Rats were randomly assigned to four dose groups as shown in the following table and orally dosed with TBX at dose levels of 0, 1250, 2500, 5000, and 10000 ppm via diet admix.

Group	Compound	Dose (ppm)	Calculated Dose (mg/kg/day)		Dosing Duration	Nº of Animals
			♂	♀		
1	Control	0	0	0	13-week	10/sex/group
2	TBX	1250	73.7	72.7		
3		2500	149.4	152.5		
4		5000	306.0	303.3		
5		10000	592.1	606.8		

The following observations were conducted.

- Mortality & Clinical Signs - 1x/day.
- Body Weight & Food Consumption - 1x/week.
- Clinical Pathology (Hematology, Clinical Chemistry and Urinalysis) - Week 13, prior to terminal sacrifice.
- Necropsy - Week 13, all surviving animals. Necropsies were performed immediately on any animals that were found dead.
  Organ Weights: Organ weight was recorded for the following organs: liver, kidneys, adrenals, testes, ovaries, brain, heart, lungs, and spleen.
  Tissues/Organs Preserved: The following organs were removed from all the animals, and stored in a 10% neutral buffered formalin solution: brain, pituitary, thyroid-parathyroid, thymus, trachea, lungs, heart, aorta, salivary glands (submaxillary glands, sublingual glands), liver, spleen, adrenals (bilateral), pancreas, testes (bilateral), epididymis (bilateral), prostate, seminal vesicle, ovaries (bilateral), uterus, vagina, skin (ventral), esophagus, stomach (proventriculus, ventriculus), duodenum, jejunum, ileum, cecum, colon, rectum, kidneys (bilateral), urinary bladder, lymph nodes (submandibular and mesenteric), mammary glands (♀ only; abdominal), muscles (femoral; unilateral), sciatic nerve (unilateral), femur (including marrow; unilateral), sternum (including marrow), eyes and accessory glands (bilateral), spine (cervical, thoracic, lumbar), and the lacrimal glands.
  Microscopic Examinations - Sections from the liver, kidneys, urinary bladder, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum of all animals were subjected to microscopic evaluations.

Results:

- Mortality & Clinical Signs - No mortality occurred. Severe weight losses were noted in animals at 10000 ppm.
- Body Weight - Significant and dose-dependent lower mean body weights (♂: ↓5-8%, 11-18%, and 46-99% for 2500, 5000, and 10000 ppm, respectively during Weeks 1→13; ♀: ↓5-6% for 1250 ppm at Weeks 5→13, ↓5-8% for 2500 ppm at Weeks 4→13, ↓5-12% for 5000 ppm and ↓24-32% for 10000 ppm at Weeks 1→13) were noted in TBX-treated ♂ @ ≥2500 ppm and ♀ @ ≥1250 ppm. These observations were in agreement with the findings for body weight gains. The accumulative 13-week weight gains for both males and females are shown in the following table.

Sex	Dose (ppm)				
	0	1250	2500	5000	10000
♂	262	231 (↓5%)	216** (↓11%)	184** (↓24%)	82** (↓66%)
♀	115	107* (↓7%)	103** (↓10%)	96** (↓17%)	64** (↓44%)

*: p≤0.5; **: p≤0.01

- Food/Water Consumption - A marked reduction in feed consumption which persisted throughout entire treatment period was noted for rats at 10000 ppm by 62%→27% for ♂ and 51→6% for ♀, respectively. Males at 5000 ppm also showed reduced food intake (↓18→7%) at the first 3 weeks of treatment. An increase in H_2O intake was noted for both ♂ (↑1.4-2.2x) and ♀ (↑1.3-1.6x) @ 10000 ppm during the entire period of study.
- Clinical Pathology - Dose-dependent ↓ in RBC (↓11-18%), hematocrit (12-15%) and Hb (11-13%) with ↑ reticulocyte counts (29-53%) were seen in rats at 10000 ppm. A significant ↓ in WBC (↓26%) and absolute segment PMN counts (↓34%) was seen in the ♂ rats at 10000 ppm. In the ♂ rats, significant ↓ urine pH (5.5-7.5 vs 7.5-8.0 in controls) concentrations were seen in the groups at ≥1250 ppm, and ↑ the frequency of occult blood (+) was noted in the groups at ≥5000

ppm. In the female rats, ↓ urine pH (6.0-7.0 vs 7.5-8.5 in controls), ↑ ketone body (5 mg/dl: 3/10; 15 mg/dl: 1/10), ↑ urine protein (30 mg/dl: 4/10; 100 mg/dl: 2/10; ≥300 mg/dl: 3/10), and ↑ occult blood (+) frequency (trace→3+: 7/10) occurred in the 10000 ppm group. Rats at 10000 ppm had ↑ urine excretion by 3.5x for ♂ and 1.6x for ♀. Urine sediment analysis revealed that ↑ RBC in the ♂ at 5000 ppm (2+/3+: 10/10) and 10000 ppm (1+→3+: 8/10) in the ♀ at 10000 ppm (1+→3+: 9/10).

- Gross and Microscopic Pathology - Decreased relative and absolute weights of testes (↓65 and 30%, respectively) and ovaries (↓41 and 21%, respectively) for ♂ and ♀, respectively, at 10000 ppm. In addition, ↑ relative liver weights (8-20%) were noted for ♂ at ≥1250 ppm. Females at 10000 ppm had ↑ relative and absolute kidney weights (↑12%). Calculi were found in the kidney, ureter, and/or urinary bladder in the animals at 10000 ppm. Enlarged kidney and ureterectasis (5♂) were found in some animals at 10000 ppm. Gross pathological examination showed slight to severe thymic atrophy (9♂ & 5♀), slight or slight to moderate atrophy of testes (9/10), epididymis (9/10), seminal vesicle (9/10) and prostate gland (9/10), slight→moderate atrophy of uterus (6/10) and ovaries (slight, 4/10), and alight to severe dilation of urinary tract (5♂ & 7♀) in animals at 10000 ppm. Significant histopathological findings included:
  - *Kidney:* Slight→severe dilation of the renal tubules (10♂ & 9♀), hyperplasia of the pelvic epithelium (9♂ & 9♀, slight→severe), and inflammation (7♂ - slight→severe & 2♀ - slight) and fibrosis (3♂ - moderate→severe, & 1♀ - slight) were detected in rats at 10000 ppm.
  - *Urinary Bladder:* Moderate→severe hyperplasia of mucosal epithelium (6♂ @ 2500 ppm; 10♂ & 3♀ @ 5000 ppm; 7♂ & 6♀ @ 10000 ppm) and inflammation with characteristics of hemorrhaging and edema with infiltration of neutrophils and lymphocytes (4♂ @ 2500 ppm; 10♂ @ 5000 ppm; 7♂ & 4♀ @ 10000 ppm) were identified.
  - *Others:* Granuloma in the parenchyma of the liver was detected in 1♀ at 5000 ppm and calcification in the muscle layer of the stomach was noted in one control female.

3.2.2.3. BMY-26517 (TBX): 13-Week Oral Subacute Toxicity Study in Rats. (SR2104)(Vol. 1.20, p 217)

Report Nº: SR2104
Study Nº: NRILS 83-1001
Study Aims: To assess the potential of TBX to induce sub acute toxicity in rats following 13-week oral administration.
Compound: Pemirolast Potassium (TBX) (Lot Nº 821206, 830117, and 830119, purity≥98%) powder
Dose & Route: 0, 5, 10, 50, and 250 mg/kg po qd by gavage for 13 weeks followed by a 5-week recovery (without dosing) phase

Group	I	II	III	IV	V
Dose (mg/kg/day)	0	5	10	50	250
Dosing Duration	13-Week				
Recovery Phase	5-Week				
Nº of Animals	22*/sex	15/sex	15/sex	22*/sex	22*/sex

* 7/sex were allowed to have a 5-week recovery period.

Animal: Crj:CD(SD) rats, ~6-week of age, weighing 165-194 g for ♂ and 124-145 g for ♀
Compliance with GLP/QAU: Yes
Study Site:
Study Date: 1/5/1983 - 2/24/1984
Dosing Initiation Date: 3/1/1983

Necropsy Date: 7/7/1983

Study Designs: Rats were randomly assigned to 5 dose group and given various doses of TBX for 13 weeks as shown in the above table. Seven/sex from Groups 1, 4, and 5 were allowed to have a recovery phase. The following observations were conducted.

- General Condition and Mortality - 1x/day.
- Body Weight - Weeks 1-4, 2x/week and Weeks 5-18, 1x/week.
- H_2O and Food Intake - 1x/week.
- Ophthalmoscopic Examination - Day 84, 8 rats/group; Day 28 of recovery phase, 4 rats/group.
- Laboratory Pathology -
  Urinalysis - ♂: Days 85-90 and Days 29-30 of recovery phase; ♀: Days 85-88 and Days 29-31 of recovery phase.
  Hematology and Serum Chemistry - Week 13 prior to necropsy.
- Necropsy - Weeks 13 and 18 (recovery sacrifice).
  Organ Weights: Organ weight was recorded for the following organs: brain, hypophysis, thymus, thyroid (R only), submaxillary glands (including sublingual glands), lungs, heart, liver, spleen, adrenals, kidneys, testes, epididymides, prostate, seminal vesicles, ovaries, uterus, and carcass.
  Tissues/Organs Preserved: The following organs were removed from all the animals, and stored in a 10% neutral buffered formalin solution: brain, pituitary, thyroid-parathyroid, thymus, larynx, tongue, trachea, lungs, heart, aorta, salivary glands (submaxillary glands, sublingual glands), liver, spleen, adrenals (bilateral), Harder's gland, pancreas, testes (bilateral), epididymis (bilateral), prostate, seminal vesicle, ovaries (bilateral), uterus, vagina, skin (ventral), esophagus, stomach (proventriculus, ventriculus), duodenum, jejunum, ileum, cecum, colon, rectum, kidneys (bilateral), urinary bladder, lymph nodes (submandibular and mesenteric), mammary glands (♀ only; abdominal), muscles (femoral; unilateral), sciatic nerve (unilateral), femur (including marrow; unilateral), sternum (including marrow), eyes and accessory glands (bilateral), spine (cervical, thoracic, lumbar), and the lacrimal glands.
  Microscopic Examinations - Sections from above listed organ/tissues of all animals were subjected to microscopic evaluations.

Results:

- Mortality & Clinical Signs - Four deaths (1♂ @ 0 on Day 43 and 3♂ @ 250 mg/kg on Days 13, 39, and 61, respectively) occurred. Dosing error was the cause of 2 deaths (1 @ 0 and 1 @ 250 mg/kg). Salivation and soft stools were seen in both ♂ & ♀ at 250 mg/kg during the early stage of dosing.
- Body Weight, Food/Water Consumption - Male rats at 250 mg/kg showed marked suppression of cumulative (Day 0-90) weight gain by 18% accompanied with lower mean body weight (↓5-11%) during the treatment and the 1st three weeks of recovery phase. Decreased food intake (↓8-9%) at Weeks 1-2 and ↑ H_2O uptake (↑13-68%) from Weeks 2 to 17 (4 wk after drug withdraw) were observed in these animals.
- Laboratory Pathology - Urinalysis performed at the end of treatment revealed a ↓ in urine specific gravity (1.045 vs 1.051 in controls), an ↑ in the urine volume (15.4 vs 6.5 ml/rat/16 hr) & turbidity, a (+) occult blood (4/15) and an ↑ in the frequency of the appearance of epithelial cells (12/15 vs 7/15 in controls) for the ♂ at 250 mg/kg. Increased urine volume (12.5 vs 8.4 ml/rat/16 hr) & turbidity was noted for the ♀ at 250 mg/kg and ↑ urine specific gravity (1.046-1.052 vs 1.033) was seen for the ♀ at ≥10 mg/kg. At the end of Week 13, blood chemistry analysis showed ↑ in total bilirubin (1.9x), GTP activity (1.3x), and creatinine (1.4x) and ↓ in glutathione (↓26%) and NEFA (↓35%) in ♂ at 250 mg/kg; ↑ total bilirubin (1.6x) & ↓ glutathione (↓25%) in ♀ @ 250 mg/kg.

- Pathology - Slightly increased absolute (♂: ↑4-7%; ♀: ↑13%) and/or relative liver weight (♂: ↑7-18%; ♀: ↑20%) was seen in the rats @ 250 mg/kg. In addition, ↑ spleen weight (↑17%), ↓ thymus weight (↓33%), and ↓ testicular weight (5-6%) were noted for the ♂ at 250 mg/kg. In the ♀ at 250 mg/kg, ↑ the relative (10%)/absolute (18%) weight of submaxillary gland was also observed. Gastric ulcer (9/14♂ & 2/15♀), enlarged kidney (2/14♂), and yellowish-white crystalline calculi in the bladder (4/14♂) were observed in the animals at 250 mg/kg. Urinary bladder calculi could be found in the 1/5♂ at 250 mg/kg even at the end of recovery phase. The following microscopic lesions were identified at the end of 13-week treatment:
  - *Kidney:* anemic glomeruli (4♂ @ 250 mg/kg); dilatation of proximal renal tubules (2♂ @ 250 mg/kg & 1♀ @ 50 mg/kg), distal renal tubules (5♂ & 3♀ @ 250 mg/kg, 1♂ @ 5 mg/kg) or collecting tubule (4♂ & 1♀ @ 250 mg/kg); transitional epithelium hyperplasia (7♂ & 1♀ @ 250 mg/kg).
  - *Urinary Bladder:* transitional epithelium papillary hyperplasia with cellular infiltration (9♂ @ 250 mg/kg).
  - *Stomach:* mucosal epithelium ulceration (11♂ & 2♀ @ 250 mg/kg; 1♂ @ 5 mg/kg; 1♂ & 1♀ @ 0 mg/kg)

  The histopathological changes, except a mild transitional papillary hyperplasia (2/5♂), were not found in the animals at 250 mg/kg at five weeks after withdrawal of treatment.

3.2.2.4. BMY-26517: 13-Week Oral Subacute Toxicity Study with a 5-Week Recovery Phase in Dogs. (SR2147)(Vol. 1.21, p 1)

13-Week Oral Subacute Toxicity Studies Followed by Five-Week Recovery Tests of TBX in Beagles. Jpn Pharmacol Ther. 1989; 17(4): 1153-1181. (SR2147-P)(Vol. 1.21, p 311)

Report Nº: SR2147
Study Nº: SBL 85-09
Study Aims: To determine the oral toxicity of TBX in dogs after 13 weeks administration followed by a 5-week recovery period.
Compound: Pemirolast Potassium (Lot Nº M-06) in capsule
Dose & Route: 0, 10, 50, and 150 mg/kg po for 13 weeks followed by a 5-week recovery (without dosing) phase
Animal: 20♂ & 20♀ beagles, 6-8 months old, weighing 6.5-8.7 kg for ♂, 5.9-8.2 kg for ♀, 4-6/sex/group
Compliance with GLP/QAU: Yes
Study Date: 3/12/1986 - 4/3/1987
Study Site:

Study Designs: Groups of 4-6/sex dogs were randomly assign to 4 groups and orally given TBX in the capsule as indicated in the following table.

Group	Compound	Dose (mg/kg)	Route	Dosing Duration	Nº of Animals	Recovery Phase
1	Control	0	Oral	13-Week	4-6*/sex/group	5-Week
2	TBX	10				
3		50				
4		150				

* 2/sex from Groups 1 and 4 were allowed to have a 5-week recovery phase.

The following observations were monitored.

- Clinical Signs and Mortality - 3x/day.

- Food Consumption - 1x/day.
- Body Weight and H_2O Intake - 1x/week.
- Body Temperature & Pulse Rate - 1x/week.
- Ophthalmologic Examination - visual observation, 1x/day; slit-lamp, Weeks -1, 13, and 18 (the end of recovery phase); ERG, Weeks -1, 5, 13, and 18, 2/sex/group.
- ECG (Lead I, II, II and V_R V_L, and V_F) - Weeks -1, 13, and 18 (the end of recovery phase).
- Clinical Pathology (Hematology, Serum Chemistry, Urinalysis, and Fecal Occult Blood) - Weeks -1, 13, and 18 (the end of recovery phase). The following parameters were analyzed.

HEMATOLOGY		SERUM CHEMISTRY				URINALYSIS	
RBC		ALT	AST	Inorganic Phosphorus		Appearance	pH
WBC with Differential		Albumin	A/G Ratio	Total Bilirubin		Bilirubin	Na
Ht	Hb	ALP		Total Cholesterol		Protein	K
MCV	MCHC	LDH	FDP	Glucose	Creatinine	Glucose	Cl
MCH	Fibrinogen	LAP	CPK	Total Protein		Specific Gravity	Total Volume
Platelet Count		Sodium	Potassium	γ-Glutamyltransferase		Ketones	Urobilinogen
Reticulocyte Count		Calcium	Globulin	Triglycerides		Occult Blood	
PT	aPTT	BUN	Uric Acid	Glutathion		Microscopic Examination of Sediment	

- Gross & Microscopic Pathology - Weeks 13 (terminal sacrifice) and 18 (recovery phase sacrifice, 2/sex from Groups 1 and 4).

  Organ Weight - The absolute weights of the cerebrum, cerebellum, pituitary, thyroid (R + L), heart, lungs, liver, adrenals (R + L), kidneys (R + L), spleen, testes (R + L), prostate, epididymis (R + L), ovaries (R + L), uterus, submaxillary glands (R + L), thymus and urinary bladder of all cases in each group were measured and recorded.

  Histopathology - In addition to the lists of organs as previously mentioned for organ weight measurement, the eyeballs (including optic nerve), tongue, trachea, bronchi, gallbladder, pancreas, vagina, esophagus, stomach (corpus and pylorus), small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), bone marrow and bones (sternum and femur), aorta, mesenteric lymph nodes, skin, mammary glands, submaxillary lymph nodes, parathyroid, brain stem, spinal cord, sciatic nerve, gross lesions, and skeletal muscles (quadriceps) were preserved in 10% neutral formalin solution (the eyeballs were fixed with Bouin's solution). Sections from these tissues/organs were subjected to microscopic examination.

  Electron Microscopy - Part of the liver and kidneys from 2/sex in Groups 1, 3, and 4 and all animals of the recovery phase were processed for electronic microscopic examination.

Results:

- Clinical Signs and Mortality - Two ♂ & 1♀ at 150 mg/kg died on Days 28, 32, and 36, respectively and 1♀ at 150 mg/kg was sacrificed on Day 41 with signs of lowered body temperature, nasal hemorrhages, tarry stools, dislocation of the crystalline lens, and tremors. Vomiting, reddening of the conjunctiva, palpebral sebum, decreased spontaneous movements, corneal turbidity, wasting, and dehydration were major signs for the animals at 150 mg/kg during the treatment.
- Body Weight, Food and H_2O Consumption - A decrease in food (♂: ↓16-52% during Weeks 2→5; ♀: ↓7-53% during Weeks 1→6) and H_2O intake (♂: ↓50-61% during Weeks 2→4; ♀: ↓42-61% during Weeks 2→5) accompanied by body weight loss was seen in the dogs at 150 mg/kg that died or that were sacrificed during treatment. Mean body weights (±SD) of ♂ and ♀ dogs in each group during the treatment period are shown in the following table.

Week	Control		10 mg/kg/day		50 mg/kg/day		150 mg/kg/day	
	♂	♀	♂	♀	♂	♀	♂	♀
-1	7.67±0.72	7.05±0.75	7.45±0.87	6.88±0.59	7.60±0.68	6.85±0.60	7.65±0.53	7.00±0.52
1	7.95±0.71	7.27±0.76	7.75±0.79	7.10±0.45	7.93±0.69	7.15±0.52	7.97±0.48	7.17±0.65
2	8.07±0.73	7.35±0.69	7.60±0.99	7.10±0.45	7.98±0.62	7.30±0.63	7.35±0.85	6.67±0.94
3	8.40±0.76	7.67±0.60	8.05±1.05	7.25±0.53	8.25±0.74	7.63±0.67	7.02±1.55	6.43±1.34
4	8.70±0.77	7.92±0.65	8.28±1.17	7.45±0.52	8.53±0.81	7.95±0.66	6.82±2.02	6.25±1.75
5	8.83±0.76	7.97±0.67	8.28±1.24	7.58±0.64	8.65±0.75	8.10±0.70	8.13±1.15	6.15±2.12
6	8.90±0.77	8.05±0.62	8.43±1.28	7.63±0.71	8.75±0.87	8.23±0.70	8.40±1.02	7.50±1.17
7	9.00±0.86	8.20±0.61	8.48±1.35	7.73±0.81	8.83±0.98	8.38±0.78	8.58±1.02	7.75±1.05
8	9.22±0.95	8.35±0.64	8.60±1.41	7.90±0.84	9.03±1.10	8.63±0.78	8.80±0.78	8.03±0.91
9	9.32±0.98	8.47±0.58	8.73±1.39	7.95±0.60	9.08±1.07	8.68±0.74	8.83±0.83	8.05±0.79
10	9.58±0.99	8.67±0.65	8.98±1.51	8.15±0.83	9.33±1.11	8.96±0.78	9.15±0.79	8.40±0.65
11	9.77±0.93	8.80±0.67	9.08±1.50	8.15±0.81	9.33±1.23	8.90±0.82	9.13±0.78	8.40±0.70
12	9.77±0.85	8.83±0.71	9.23±1.53	8.33±0.71	9.53±1.23	9.05±0.87	9.23±0.70	8.45±0.73
13	10.08±0.87	9.02±0.81	9.53±1.56	8.50±0.69	9.80±1.10	9.30±0.92	9.48±0.99	8.63±0.68

- Body Temperature & Pulse Rate - Decreases in body temperature and bradycardia/tachycardia were noted for the high dose animals that died or were sacrificed. One each of surviving high dose ♂ and ♀ had transient bradycardia/tachycardia with weight loss and showed loss appetite.
- Ophthalmologic Examination - In addition to the abnormalities seen in the cornea (turbidity) and lens (discoloration), ↓ amplitude of a-waves, b-waves and o-waves was identified in the ERG test performed on Week 5 for the animals at 150 mg/kg. At week 13 examination, the decreases in amplitude for the a-, b-, o-waves were less pronounced; by Week 5 of recovery period, the waves returned to normal levels. No abnormal changes were noted in the fundus analysis.
- ECG - Normal.
- Clinical Pathology - Fecal occult blood test was conducted in the survival animals and no abnormalities were detected. Urinalysis revealed mild positive ketone (±) and proteinuria (±) in the urine obtained from the ♀ at 150 mg/kg that died or was sacrificed during the study. Hematological analyses showed significantly ↓ RBC (♂: ↓23 and 17%; ♀: ↓23 and 17%, respectively), Ht (♂: ↓20 and 7%; ♀: ↓24 and 12%, respectively) and Hb (♂: ↓23 and 7%; ♀: ↓23 and 12%, respectively) for the ♂ and ♀ @ 150 mg/kg at Weeks 5 & 13. Elevated LDH was seen in ♂ & ♀ @ 150 mg/kg (312-330 IU/l vs 129-161 IU/l in controls) at Week 5 blood chemistry analysis. **No data for each individual animal were submitted.**
- Gross & Microscopic Pathology - High dose ♂ had ↓ in the absolute and relative weights of the testes during terminal sacrifice (↓74 and ↓71%, respectively) and recovery sacrifice (↓24% and ↓23% respectively). Corneal turbidity or congestion, and dark reddening of the duodenum were noted in the dogs at 150 mg/kg that died or were sacrificed during the dosing period. Gross examination showed dislocation of the crystalline lens with lesions of necrosis and hemorrhage, ulceration of gastric mucosa, thymic atrophy, dark reddening of mesenteric lymph nodes, enlarged thyroid, and pale mucosa. No changes were noted in animals that survived to the end of 13-week study or to the end of the recovery period. Microscopic lesions characterized as pulmonary edema, mild localized pneumonia foci, slight atrophy of the spleen, hyperplasia of the red pulp, moderate atrophy of the prostate epididymis, and testes with decreased sperm, erosion or ulcers or congestion in the GI tract, and atrophy of bone marrow and mesenteric lymph nodes were seen in the dogs at 150 mg/kg that died or were sacrificed during the dosing period. Atrophy of the spleen and submaxillary lymph nodes was also identified in dogs at 50 mg/kg. Decreased sperm and atrophy of the reproductive organs were observed in the ♂ @ 150 mg/kg during the terminal sacrifice.
- Electron Microscopy - No abnormalities were identified in the ultrastructures of liver and kidneys.

3.2.3. CHRONIC TOXICITY

3.2.3.1. BMY-26517 (TBX): 52-Week Chronic Oral Toxicity Study in Rats Toxicity. (SR2141)(Vol. 1.22, p 001)

Report Nº: SR2141
Study Nº: NRILS 86-1730
Study Aims: To determine the potential of TBX to induce chronic toxicity in rats following 52 weeks oral administration.
Compound: Pemirolast Potassium (TBX) (Lot Nº M-08) powder
Dose & Route: 0, 2, 10, 50, and 150 mg/kg/5 ml/day po for 52 weeks by oral gavage
Vehicle: Dist. H_2O for injection
Animal: Crj:CD(SD) rats, ~6-week of age, weighing 137-159 g for the ♂ and 120-140 g for the ♀, 20/sex/group
Compliance with GLP/QAU: Yes (Japanese)
Study Date: 3/10/1986 - 6/17/1988
Study Site:

Study Designs: Groups of 20/sex rats were randomly assigned to 5 groups and dosed with various levels of TBX for 52-week as indicated in the following table.

Group	Compound	Dose (mg/kg)	Route	Dosing Duration	Nº of Animals
1	Control	0	Oral (Gavage)	52-Week	20/sex/group
2	TBX	2			
3		10			
4		50			
5		150			

The following parameters were conducted.

- Clinical Signs and Mortality - ≥1x/week.
- Body Weight, H_2O & Food Consumption - 1x/week for Weeks 1→12/13 and 1x/4 weeks thereafter.
- Ophthalmologic Examination - Pre-R and Weeks 27 and 51.
- Clinical Pathology - Urinalysis, Weeks 26 and 51; Urine Crystal Examination: ≥½ of surviving Group 5 animals only, Weeks 14 and 40; Hematology and Serum Chemistry: at the end of study (prior to terminal sacrifice). The following parameters were analyzed.

HEMATOLOGY		SERUM CHEMISTRY			URINALYSIS	
RBC		ALT	AST	Inorganic Phosphorus	Appearance	pH
WBC with Differential		Albumin		Total Bilirubin	Bilirubin	Na
Ht	Hb	A/G Ratio		Total Cholesterol	Protein	K
MCV		LAP (Leucine Amino Peptidase)		Glucose	Glucose	Cl
MCHC		NEFA (Acyl CoA Synthetase/Oxidase)			Specific Gravity	
MCH		ALP	CPK	Total Protein	Urine Crystal Determination	
Platelet Count		Sodium	Potassium	LDH	Urobilinogen	Ketones
Reticulocyte Count		Creatinine		Triglycerides	Occult Blood	
Fibrinogen Conc.		Calcium		Globulin	Total Volume	
PT	aPTT	BUN	Uric Acid	Glutathion	Microscopic Examination of Sediment	

- Necropsy - Week 52/53.
  Organ Weight: The brain, pituitary gland, thymus gland, thyroid gland (R only), submaxillary glands, lungs, heart, liver, spleen, adrenal glands, kidneys, testes, epididymis, prostate gland, ovaries, and uterus were weighed.

Histopathology: In addition to the organs mentioned above, the pancreas, stomach, duodenum, jejunum, ileum, colon, rectum, submaxillary lymph nodes, mesenteric lymph nodes, mammary glands (♀ only), trachea, parathyroid gland, tongue, esophagus, vagina, Harderian gland, spinal cord, sciatic nerve, femoral muscle, skin (back), bone marrow of the femur, testicles, bladder, gross lesions and eyeballs (both eyeballs were taken when abnormalities were found during the ophthalmological examination; the left eye included the vitreous body) were fixed with 10% neutral buffered formalin solution (the OD was fixed with Bouin's solution, the OS was fixed with modified Bodeian's solution). Sections from these organs/tissues were subjected microscopic examination. The histological examinations were also performed on dying or dead animals whenever possible (in which cases only the left eye was removed and fixed).

Electron Microscopy: Parts of the kidney and liver from 2/sex in the control group and all dosage groups, which were removed for the histopathological examination, were processed for electron microscopic examination.

Results:

- Mortality & Clinical Signs - Mortality of each group is presented in the following table.

Mortality	Dose (mg/kg/day)				
	0	2	10	50	150
♂	2/20	2/20	1/20*	1/20	0/20
♀	2/20	2/20	0/20	0/20	1/20

* Sacrificed at moribund.

The cause of death for 5/6♂ was due to dosing error. Weight loss was the common finding for the animals that died during the study. None of the survivals exhibited overt clinical signs.

- Body Weight, H_2O & Food Consumption - Lower mean body weight (↓9-17% at Weeks 16→52), decreased cumulative (Weeks 0-52) weight gain by 21%, ↑ water intake (15-65% at Weeks 6 →49) were noted in ♂ at 150 mg/kg/day. A transient ↑ (12%) in food intake in the ♂ at 150 mg/kg at Week 33.
- Ophthalmologic Examination - No significant treatment-related findings were identified.
- Clinical Pathology - An increase in urine volume (2.6x) for the ♂ @ 50 and 150 mg/kg at Week 26 postdosing, a decrease in urine specific gravity for the ♂ @ 150 mg/kg at Weeks 26 & 51 postdosing (1.047 vs 1.057 and 1.04 vs 1.055, respectively), ↑ the presence of RBC (3+, 8/10) and round cells (3+, 1/10) in the urine sediment of the ♂ @ 150 mg/kg at Week 51 postdosing, and crystalline urine in 3/10, 1/10, 5/10, 9/10 ♂ @ 150 mg/kg at Weeks 14, 26, 40, and 51, respectively were the major significant findings at urinalysis. Significant differences between controls and TBX-treated rats in the hematological examination at final sacrifice were ↑ reticulocytes for the ♀ @ 50 & 150 mg/kg, ↑ platelet counts for the high dose ♀, ↑ RBC and ↓ MCV values for the ♂ @ 50 mg/kg, and ↑ MCHC for the high dose ♂. These differences were not dose-related, and the values were within normal biological ranges. There were no biological significant changes were noted in the all analyzed clinical chemistry parameters.
- Gross & Microscopic Pathology - Calculi were found in the urinary bladder of 17/20♂ @ 150 mg/kg. The increased relative weight of brain (↑20%), submandibular salivary glands (↑30%), lungs (↑24%), heart (↑17.6%), liver (↑19%), kidneys (↑20%), adrenals (↑23%), testes (↑24%), and epididymides (26%) were observed in ♂ at 150 mg/kg. An ↑ in relative organ weight of liver, spleen and liver/spleen was observed in ♂ @ 50 mg/kg (↑9%), ♀ @ 50 mg/kg (↑19%) and ♀ at 150 mg/kg (↑15-17%), respectively. Treatment-associated microscopic lesions were identified in the following organs:
  - *urinary bladder*: papillomatosis (13), transitional cell hyperplasia (2) and carcinoma (2) and hemorrhages (4), mild cellular infiltration (1) in the high dose ♂; and

- *kidney*: dilation of the distal renal tubules (7♂ @ 150 mg/kg).

3.2.3.2. BMY-26517 (TBX): 52-Week Oral Chronic Toxicity Study of TBX in Beagles. (SR2144)(Vol. 1.22, p 231)

Chronic Toxicity Study of TBX in Beagles Administered Orally for 52 Weeks. Jpn Pharmacol Ther 1989; 17(4): 1183-1204. (SR2144-P)(Vol. 1.23, p 149)

Report Nº: SR2144 & SR2144-P
Study Nº: SBL85-05
Study Aims: To determine the potential of TBX to induce chronic toxicity in dogs after 52 weeks oral doing.
Compound: Pemirolast Potassium (Lot Nº M-10) in gelatin capsules
Dose & Route: 0, 2, 10, 50 and 75 mg/kg
Dosing Duration: 52-week
Animal: 20♂ & 20♀ beagles, ~6 months old, weighing 6.1-8.5 kg for ♂, 6.0-7.7 kg for ♀, 4/sex/group
Compliance with GLP/QAU: Yes (Japanese)
Study Date: 12/6/1986 - 8/9/1988
Study Site:

Study Designs: Groups of 4/sex dogs were orally dosed with TBX at various levels as shown in the following table.

Group	Compound	Dose (mg/kg)	Route	Dosing Duration	Nº of Animals
1	Control	0	Oral	52-Week	4 sex/group
2	TBX	2			
3		10			
4		50			
5		75			

The following observations were recorded.

- General Condition - 3x/day.
- Food & Water Intake, Body Weight, Body Temperature and Pulse Rate - 1x/week.
- Ophthalmological Studies - Macroscopic examination was done on a daily basis. The conjunctiva, iris, sclera, cornea, and pupillary reactions were checked for abnormalities on Weeks -1, 26, and 52 using a slit lamp. ERG were performed on dogs (2/sex) from each group on Weeks -1, 26 and 52.
- ECG - Pre-R and Week 52 on 2/sex from each group.
- Clinical Laboratory Studies - Fecal occult blood, urinalyses, hematology and clinical chemistries were done on Weeks -1, 13, 26, 39, and 52. The following parameters were analyzed.

HEMATOLOGY		SERUM CHEMISTRY			URINALYSIS	
RBC		ALT	AST	Inorganic Phosphorus	Appearance	pH
WBC with Differential		Albumin		Total Bilirubin	Bilirubin	Na
Ht	Hb	A/G Ratio		Total Cholesterol	Protein	K
MCV		ALP		Glucose	Glucose	Cl
MCHC		LDH	Triglycerides	Creatinine	Specific Gravity	
MCH		LAP	CPK	Total Protein	Ketones	
Platelet Count		Sodium	Potassium	γ-Glutamyltransferase	Urobilinogen	
Reticulocyte Count		FDP (Fragment Degradation Product)			Occult Blood	
Fibrinogen Conc.		Calcium		Globulin	Total Volume	
PT	aPTT	BUN	Uric Acid	Glutathion	Microscopic Examination of Sediment	

- Pathology - Necropsy was performed on each animal at the end of study.
  Organ weights: The absolute weight of the heart, spleen, thymus, lungs, liver, kidneys, bladder, testes, epididymis, prostate, ovaries, uterus, pituitary, thyroid, adrenals, cerebrum, cerebellum, and submaxillary glands was determined.
  Histopathology: The following organs/tissues were preserved in 10% neutral formalin: heart, aorta, spleen, thymus, bones and marrow (femur and sternum), mandibular lymph nodes, mesenteric lymph nodes, trachea, bronchial tubes, lungs, tongue, esophagus, stomach (body and pyloric part), small intestines (duodenum, jejunum, ileum), large intestines (cecum, colon, rectum), pancreas, liver, gallbladder, kidneys, bladder, testes, epididymis, prostate, ovaries, uterus, vagina, pituitary, thyroid, parathyroid, adrenals, cerebrum, cerebellum, brain stem, spinal cord, sciatic nerves, eyes (including optic nerves), skeletal muscles (quadriceps muscle of the thigh), skin, mammary glands, gross lesions, and submaxillary glands. Eyes were fixed with Bouin's solution. All specimens were subjected to microscopically studied.
  Electron Microscopy: Parts of the liver and kidneys from 2/sex/group were fixed with OsO_4 and processed for electron microscopic examination..

Results:

- General Condition - No deaths occurred. Vomiting was the major clinical observation. Eye discharge and soft stools were seen occasionally.
- Food & Water Intake, Body Weight, Body Temperature and Pulse Rate - Reduced food intake during Week 9 in 1♀ @ 75 mg/kg/day was noted by the sponsor; however, **no data were presented**. Significant higher mean weight values (↑25-30%) were seen in ♀ @ 2 mg/kg/day during the weeks 43-45 and 52. A slight increase (8-9%) in pulse rates was observed in ♀ @ 75 mg/kg/day during weeks 19-21 and 33.
- Ophthalmological Studies - No significant changes were noticed.
- ECG - No abnormalities were detected.
- Clinical Laboratory Studies - Occasionally urine protein was detected in a few animals of each group. No dose-related incidence was observed.
- Pathology - Minimal hepatic congestion (2), cystic pituitary lesions (2), splenic congestion (1) and hepatocellular vacuolation (1) were seen in ♂ @ 75 mg/kg.

3.3. CARCINOGENICITY

3.3.1. RAT STUDY

3.3.1.1. BMY-26517 (TBX): Carcinogenicity by Dietary Administration in Rats. (SR2107)(Vol. 1.25-26 and Vol. 3.1-3.3)

Report Nº:	SR2107
Study Nº:	6K088
Study Aims:	To determine carcinogenic potential of TBX following oral administration to rats for 2 years.
Compound:	Pemirolast Potassium (Lot Nº M-07 & M-10)
Dose & Route:	0, 70, 200, and 625 ppm po via diet admix
Dosing Duration:	104-week
Animal:	♂ & ♀ F344/DuCrj rats, 5-week-old, weighing 88-107 g for ♂ and 78-92 g for ♀.

Group	Dose (ppm) in the Diet	Dose (mg/kg)		Duration (week)	Route	N° of Animals	
		♂	♀			♂	♀
Control	0	0	0	104-week	Oral	50	50
Low	70	2.87	3.29			50	50
Medium	200	8.28	9.39			50	50
High	625	26.1	30.0			50	50

Compliance with GLP/QAU: Yes
Dosing Initiation: 3/10/1986
Terminal Sacrifice: 8/26 & 29-30/1988 for ♂; 8/18-19 & 22/1988 for ♀.
Study Site:

Study Designs: Rats, 50/sex/group, were randomly allocated in to 4 groups as shown in the above table. The following parameters were monitored.

- General Condition and Mortality - 1x/day.
- Detailed Physical Examination - 1x/week.
- Body Weight - Day 0 and 1x/week up to 13 weeks, and 1x/3-4 weeks thereafter.
- Food Consumption - 1x/week up to 13 weeks and 1x/3-4 weeks thereafter.
- Clinical Pathology (**control and 625 ppm groups**) - Hematology, Weeks 52 and 78; Urinalysis Weeks 26, 52, 78 and 103.
- Necropsy - Autopsy was done on every animal.

  Organ Weight: The wet weight of the following organs was determined for the final sacrificed animals as well as for unscheduled deaths: liver, kidneys, adrenals, testes, ovaries, brain, heart, lungs, and spleen.

  Organ Collection and Preservation: The following organs were collected from all animals, including unscheduled deaths, and preserved in a neutrally buffered 10% formalin solution: brain, pituitary, thyroid/parathyroid, thymus, trachea, lungs, heart, aorta, salivary glands (submandibular, sublingual), liver, pancreas, adrenals (bilateral), spleen, testes (bilateral), epididymis (bilateral), prostate, seminal vesicles, ovaries (bilateral), uterus, vagina, skin (ventral), tongue, esophagus, stomach (proventriculus, glandular), duodenum, jejunum, ileum, cecum, colon, rectum, kidneys (bilateral), urinary bladder, lymph nodes (submandibular, mesenteric), mammary glands (♀ only; abdominal), muscles (femoral, unilateral), femur (including marrow; unilateral), sciatic nerve (unilateral), sternum (including marrow), eyeballs and glands (bilateral), spine (cervical, thoracic, lumbar), accessory lacrimal glands, sites of macroscopic anomalies (including boundaries with healthy tissue and adjacent lymph nodes when tumors were present, whenever possible), and all tumors or morbid changes suspected of being tumors that could be seen macroscopically.

  Histopathology: Histopathological studies were performed on the tissues listed above from the **control and 625 ppm groups** and on the liver, lungs, kidneys, urinary bladder, and gross lesions for the 70 ppm and 200 ppm groups.

Results:

- Survivals & General Signs - The numbers of animals in each group found dead or sacrificed in moribund condition, and survivals at the end of 104 weeks are listed in the following table.

Parameters	Dose Levels (ppm)							
	0		70		200		625	
	♂	♀	♂	♀	♂	♀	♂	♀
N° of Animals Initiated	50	50	50	50	50	50	50	50
N° of Unscheduled Death	10	12	14	8	11	12	12	11
N° of Surviving Animals	40	38	36	42	39	38	38	39

Alopecia, subcutaneous and intra-peritoneal nodules, cloudy eye and lacrimation were seen in both ♂ & ♀ at different time during the course of study. TBX-treated animals showed to have subcutaneous nodules earlier than the controls during the whole course of study.

- Body Weight & Food Consumption - Animals at 625 ppm had a slight but statistical significant ↓ (♂: ↓5.5%; ♀: ↓4.4%) in mean body weights. There was no significant difference in food consumption.
- Clinical Laboratory Observation - Hematological analysis on samples obtained prior to final sacrifice showed ↑ reticulocyte counts for the ♂ at 200 ppm, ↑ Hb with ↓ platelet counts and ↑ lymphocyte counts in the ♂ at 625 ppm, and ↓ MCV in the ♀ at 625 ppm. These changes were minor and values for these parameters were within biological normal range. Urinalysis was performed on the control and rats in 625 ppm groups on weeks 26, 52, 78, and 103 weeks. No striking findings could be attributable to the treatment.
- Microscopic Pathology -
  - *Neoplastic Incidence*: Tumors were identified in 100, 100, 96, and 100% of the ♂ and 68, 54, 58, and 60% of the ♀ in the 0, 70, 200 and 625 ppm groups, respectively. Much higher Nº of ♂ at 625 ppm had more multiple tumors than the controls (82 vs 65%). Endometrial stromal polyps were found more often in the TBX treated rats with frequency of 8, 6, 16, and 22% in the control, 70, 200 and 625 ppm, respectively.
  - *Non-neoplastic incidence*: No apparent changes were drug-related.

Due to lack of effects on body weight gains, mortality and apparent pathological changes observed in the high dose group, the MTD was not reached. In addition, some tissues from 70 and 200 ppm groups were not examined; therefore, statistical analysis for the trend incidence in some tumor findings can not be performed and the study was not acceptable by current regulatory standards.

3.3.2. *MOUSE STUDY*

3.3.2.1. BMY-26517 (TBX): Carcinogenicity by Dietary Administration in Mice. (SR2108)(Vol. 1.23, p 201 - Vol. 24 and Vol. 3.4-3.7)

Report Nº: SR2108
Study Nº: 6K090
Study Aims: To determine carcinogenic potential of TBX by dietary administration to mice for 18 moths (78-week).
Compound: Pemirolast Potassium (Lot Nº M-06 & M-10)
Dose & Route: 0, 70, 200, and 625 ppm po via diet admix for
Dosing Duration: 18 months (78-week)

Group	Dose (ppm) in the Diet	Dose (mg/kg)		Duration (Week)	Route	Nº of Animals	
		♂	♀			♂	♀
Control	0	0	0	78-week	Oral	50	50
Low	70	7.27	7.21			50	50
Medium	200	20.3	21.6			50	50
High	625	65.6	69.6			50	50

Animals: B6C3F$_1$ mice, 5-week-old, weighing 18.3-21.8 g for ♂ and 15.8-19.9 g for ♀.
Compliance with GLP/QAU: Yes
Study Date: 3/10/1986 -1/1/1989
Study Site:

Study Designs: Animals were allotted in to 4 groups as shown in the above table. The following observations were conducted.

- Clinical Signs and Mortality - 1x/day.
- Detailed Physical Examination - 1x/ week.
- Body Weight and Food Consumption - Day 0, 1x/week up to 13 weeks, and 1x/3-4 weeks thereafter.
- Clinical Pathology - Hematology: Weeks 52 and 78, all surviving animals; Urinalyses: Weeks 25, 52, and 78, control and high-dose groups only.
- Necropsy - Week 78. Autopsy was done on every animal.
  Organ Weight: The following organs were weighed: liver, kidneys, adrenals, testes, ovaries, brain, heart, lungs, and spleen.
  Organ Collection and Preservation: The following organs were collected from all animals, including dead animals and animals sacrificed to hasten their death, and preserved in a neutrally buffered 10% formalin solution: brain, pituitary, thyroid/parathyroid, thymus, trachea, lungs, heart, aorta, salivary glands (submandibular, sublingual), liver (including the gallbladder), pancreas, adrenals (bilateral), spleen, testes (bilateral), epididymis (bilateral), prostate, seminal vesicles, ovaries (bilateral), uterus, vagina, skin (ventral), tongue, esophagus, stomach (proventriculus, glandular), duodenum, jejunum, ileum, cecum, colon, rectum, kidneys (bilateral), urinary bladder, lymph nodes (submandibular, mesenteric), mammary glands (females only: abdominal), muscles (femoral, unilateral), femur (including marrow: unilateral), sciatic nerve (unilateral), sternum (including marrow), eyeballs and glands (bilateral), spine (cervical, thoracic, lumbar), accessory lacrimal glands, carcass, sites of macroscopic anomalies (including the boundaries with healthy tissue and, whenever possible, adjacent lymph nodes when tumors were present), all tumors or morbid changes suspected of being tumors that could be seen macroscopically.
  Histopathology: **Microscopic examinations were performed on the above listed organs of the mice (♂ + ♀) in the control and the 625 ppm groups as well as on the liver, lungs, kidneys, urinary bladder, and gross lesions of animals at 70 ppm and 200 ppm.** Marked autolysis was found in 1 control ♀, and this animal was excluded from the histopathology examination.

Results:

- Substance Consumption - The mean values of TBX consumption in each group are presented in the above table.
- Clinical Signs and Survival Rate - No remarkable clinical signs were attributable to the treatment. There was no significant difference in the incidence of mortality between the control and TBX-treated groups. The numbers of animals found dead or sacrificed in extremis during various periods of time are shown in the following table.

Dose (ppm)	Weeks 27-52		Weeks 53-78		Terminal Sacrifice	
	♂	♀	♂	♀	♂	♀
0	0	0	0	3	50	46
70	2	1	1	4	47	45
200	1	0	1	2	48	48
625	0	0	4	2	46	48

- Body Weight and Food Consumption - No treatment-related changes in food consumption was noted. High-dose ♀ had transient lower mean body weights (↓6-7%) at Weeks 29, 35, and 42→55.
- Clinical laboratory Pathology - No remarkable changes in the hematology parameters, leukocyte differential counts, and urinalysis were attributable to the treatment.
- Gross and Histo-pathology - There were no significant finding attributable to the treatment. Due to some tissues from 70 and 200 ppm groups not being examined, statistical analysis for the trend incidence can not be performed.

Due to lack of observed adverse effects on all examined parameters, MTD was not achieved. The information provided by the current study is inconclusive and the study is not acceptable by the current regulatory standards.

3.4. REPRODUCTIVE TOXICOLOGY

3.4.1. FERTILITY AND EARLY EMBRYONIC DEVELOPMENT (SEGMENT I)

3.4.1.1. BMY-26517 (TBX): Test by Oral Administration before and in the Early Stages of Pregnancy in Rats. (SR2148)(Vol. 1.27, p 162; Vol.3.8, p 171)

Fertility Study of TBX in Rats. Jpn Pharmacol Ther 1990; 18(3): 893-920. (SR2148-P) (Vol. 1.27, p 224)

Report Nº: SR2148 & SR2148-P
Study Nº: R-112
Study Aims: To evaluate the effect of TBX on male and female fertility and early embryonic development in rats following oral dosing.
Compound: Pemirolast Potassium (TBX) (Lot Nº M-06) powder
Dose & Route: 0, 10, 50, 250 and 400 mg/kg/day po by oral gavage
Dosing Period: ♂ - 9 weeks before mating, through mating to the day before autopsy
♀ - 2 weeks before mating, through mating to Gestation Day 7
Animal: Crj:CD(SD) rats, ~6 (for the ♂)-13 (for the ♀) weeks of age, weighing 158-182 g for the ♂ and 230-299 g for the ♀, 24/sex/group
Compliance with GLP/QAU: Yes
Dosing Initiation Date: 5/14/1986 for ♂ and 7/2/1986 for ♀
Mating Starting Date: 7/16/1986
C-Section Starting Date: 8/7/1986
Study Site:
Study Designs: Groups of animals were orally dosed with different levels of TBX as shown in the following table.

Group	Dose (mg/kg/day)	Dosing Volume (ml/kg)	Dosing Duration		Nº of Animals/Group
			♂	♀	
Control	0	5	9-week before mating→mating → 1-day before autopsy	2-week prior to mating → Gestation Day 7	24/sex
Low Dose	10				
Mid-Dose	50				
Mid-High	250				
High Dose	400				

The following Parameters were conducted:

- Mortality & Clinical Signs - 3x/day.
- Body Weight & Food Consumption - premating and mating period: 2x/week for ♂ & ♀; Gestation Days 0, 4, 7, 11, 14, 17, and 21 for pregnant ♀ only; 2x/week for 3 weeks for non-pregnant ♀ after the end of mating period..
- Observation of Estrus Cycle - vaginal smear (10♀/group during premating period).
- Necropsy - Males found to have copulated at the end of mating were fasted overnight and sacrificed on the next day. Non-copulated ♀ were sacrificed on Day 21 after the end of mating

period. The following organs/tissues were weighted and preserved in 10% formalin: heart, lung, liver, kidney, spleen, testes (♂), epididymis (♂), ovary (♀), and uterus (♀).

C-Section - The pregnant ♀ were sacrificed on Gestation Day 21. Ovaries and uterus were removed and examined. The heart, lung, liver, kidney, and spleen were weighted. These organs plus ovary were preserved in 10% formalin.

- The following reproductive performance parameters were recorded.
  - Nº of corpora leutea;
  - Nº of implants;
  - placental weight;
  - Nº of viable fetuses; and
  - Nº of dead and resorbed fetuses.
- Fetal Parameters -
  - external exmaination;
  - sex;
  - body weight; andviseral (1/2 of fetuses) and skeletal (1/2 of fetuses) examinations.

Results:

- Mortality & Clinical Signs - A total of 9 deaths (1♂ @ 250 mg/kg on Day 56; 2♂ @ 400 mg/kg, one each on Days 45 & 65; 6♀ @ 400 mg/kg, one each on Days 10 & 29, 2 on Day 14, and one each on Gestation Days 6 & 7) were identified and one ♂ at 250 mg/kg was sacrificed on Day 65 post treatment. Excess salivation was the major sign for the animals at ≥250 mg/kg. Rough fur, wasting, suppressed spontaneous movement, rough respiration, and cool to touch were major clinical observations for the animals that died during the study. Reddish urine was noted in 52% of ♂ at ≥250 mg/kg.
- Body Weight & Food Consumption - Lower mean body weights (250 mg/kg: ↓4-7%; 400 mg/kg: 4.5-17.5%) accompanied by ↓ food consumption (8-23%) were seen in ♂ at doses ≥250 mg/kg from days 1-63. Females in 250 and 400 mg/kg groups had lower mean body weights during gestation. The mean body weight and weight gains during gestation period for each group are shown in the following table. Decreased food consumption was noted in ♀ in 250 mg/kg during Gestation Days 1→7 by 10-16% and 400 mg/kg from Days 1→10 prior to mating and Gestation Days 1→7 by 13-28%.

Dose	Mean Body Weight During Gestation							Body weight Gains	
(mg/kg)	GD 0	GD 4	GD 7	GD 11	GD 14	GD 17	GD 21	GD 0-7	GD 7-21
0	279.3	299.0	306.4	322.7	335.1	362.5	423.9	27.0	117.5
10	281.9	298.9	307.7	324.9	337.9	364.9	428.0	25.0	120.3
50	280.5	296.5	303.5	324.6	338.0	365.0	428.9	23.015	125.3
250	271.5	280.5**	287.0**	307.2**	320.9*	350.6*	413.6	15.5**	126.6
400	271.3	273.0**	284.4**	304.8**	318.4*	338.1**	388.6**	14.9**	104.2

GD = Gestation Day; * P≤0.05 (Significant difference from control); ** P≤0.01.

- Reproductive Performance - Females at 400 mg/kg had ↓ Nº of implantation, ↑ Nº of resorbed/dead fetuses, ↓ Nº of live fetuses and an ↑ in the placental weight. An ↑ in the placental weight was also seen the ♀ at 50 & 250 mg/kg. The following table shows mean (±SD) reproductive indices for each group.

Reproductive Indices	Dose (mg/kg/day)				
	Vehicle Control	10	50	250	400
Nº of Corpora Lutea	15.9 ±1.6	16.3±2.4	15.9±2.6	15.6±2.0	14.0±4.7
Nº of Implantation Sites	14.7±1.5	15.0±1.8	14.3±2.6	13.9±2.3	11.6±4.6*
% Pre-implantation Loss	7.9	8.5	9.6	10.9	17.4
Nº of Live Embryos	13.9±1.9	13.7±2.2	13.2±2.7	12.8±2.5	9.1±5.0**
Nº of Dead or Resorbed Fetuses	19 (5.4%)	30 (8.7%)	27 (8.2%)	26 (7.8%)	40 (21.6%)**
Nº of Early Resorption	18	28	27	25	40
Nº of Late Resorption	1	2	0	1	0
Placental Weight (g)	0.49±0.05	0.53±0.13	0.54±0.06**	0.57±0.09**	0.68±0.16**

Significantly different from control value: *p<0.05; **p<0.01.

- Pathology - A ↓ (8-18%) in the absolute epididymis weight with increased (14-26%) relative testis weight was observed for the ♂ at ≥250 mg/kg. Calculi in the urinary bladder, enlargement and pale color of kidneys were the major gross findings for the ♂ at 250 (13/22=59.1%) and 400 (18/22=81.8%) mg/kg at necropsy. High-dose ♂ (5/22) had significant higher frequency ($p \leq 0.05$) of pale color and enlarged kidney. Atrophy of testis and epididymis (only left side was examined) was observed in one at 10 mg/kg. No abnormality was observed for all the survival ♀.
- Fetal Development - No significant findings in visceral examination were attributable to the treatment. A slight increase in the incidence of reduced ossification of cervical rib was noted during skeletal examination with values of 0.6% (1/173), 1.2% (2/163), 1.9% (3/157), 1.9% (3/161), and 3.9% (3/76) for 0, 10, 50, 250, and 400 mg/kg groups, respectively.

Therefore, the lowest no-observable-adverse-effect-level (NOAEL) for parental, reproductive and developmental toxicities in the present study were 50, 50 and 400 mg/kg/day, respectively.

3.4.2. *TERATOGENICITY STUDIES (SEGMENT II)*

3.4.2.1. BMY-26517 (TBX): Teratology Study in Rats. (SR2149)(Vol. 1.27, p 291; Vol.3.8, p 1)

Teratogenicity Study of TBX in Rats. Jpn Pharmacol Ther 1990; 18(3): 921-958. (SR2149-P)(Vol. 1.28, p 1)

Report Nº: SR2149 & SR2149-P

Study Nº: R-069

Study Aims: To determine the possible teratogenic effects of TBX in rats following repeated oral dosing.

Compound: Pemirolast Potassium (TBX) (Lot Nº M-06) powder, dissolved in H_2O

Dose & Route: 0, 10, 50, 250 and 400 mg/kg/day, 0.5 ml/100 g po for 11 days (GD 7→17) by oral gavage

Animal: 50♂ & 200♀ Crj:CD(SD) rats, ~11 (♂)-12 (♀) weeks of age, 36-37 pregnant ♀/group

Compliance with GLP/QAU: Yes

Testing Period: 6/1/1984 - 12/9/1984; 1st Dosing, 7/31/1984; C-section Date, 8/14/1984

Study Site:

Study Designs: Groups of rats were dose with various of dosages of TBX by oral gavage from Gestation Days 7 to 17 as shown in the following table.

Group	Dose (mg/kg/day)	Dosing Volume (ml/kg)	Dosing Duration	Nº of Animals/Group
Control	0	5	Gestation Day 7→17	36-37 mated ♀
Low Dose	10			
Mid-Dose	50			
Mid-High	250			
High Dose	400			

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weight - Gestation Days (GD) 0, 7, 9, 11, 13, 15, 17, and 20; Lactation Days (LD) 0, 4, 7, 11, 14, 17, and 21.
- Food Consumption - GD 1, 4, 8, 11, 14, 17, and 20; LD 1, 4, 7, 11, 14, 17, and 21.
- C-Section (Fetal Examination) - GD 21, 2/3 of copulation-confirmed ♀ from each group. Ovaries and uterus were removed and examined. The following reproductive performance and fetal parameters were recorded. The heart, lung, liver, kidney, and spleen were weighted. These organs plus ovary were preserved in 10% formalin.
  - Nº of corpora leutea;
  - Nº of implants;
  - placental weight;
  - Nº of viable fetuses;
  - Nº of dead and resorbed fetuses;
  - external exmaination;
  - sex;
  - body weight; and
  - viseral (1/2 of fetuses) and skeletal (1/2 of fetuses) examinations

- Neonatal Examination (Natural Delivery) - Approximately 1/3 of copulation-confirmed ♀ were allowed to deliver naturally and allowed to nurse newborns for 21 days. The gestation period was recorded. On LD 21, all F_0 dams were sacrificed. The heart, lung, liver, kidney, ovaries and spleen were weighted. The uterus was examined for the Nº of implantation traces, weighed, and preserved in 10% formalin. The following parameters were recorded for the newborns:
  - litter size;
  - Nº of stillbirths;
  - external malformations;
  - sex; and
  - body weight - 2x/week to Post Natal Day (PND) 21, 1x/week to PND 70.
  - mortality - 1x/day up to PND 70.
- Differentiation Examination of Newborns - On PND 4, 4/sex newborns from each litter were randomly selected and remaining newborns were sacrificed. The following parameters were examined for the development and differentiation of the newborns. When differentiation was noted 1st examination, no 2nd examination was attempted.
  - detachment of the pinna - PND 4;
  - growth of hair - PND 7-11;
  - eruption of incisors - PND 11 and 14;
  - seperation of eyelids - PND 14 and 17;
  - decent of the testes - PND 21 and 28;
  - vaginal opening - PND 35 and 42.

- F_1 Behavior and Functional Tests - Three/sex from each litter were selected and weaned. The remaining (1/sex) animals were sacrificed and the hearts, lungs, liver, kidneys, spleen, and testes or ovaries were weighed and preserved in 10% formalin. The following tests were carried out in 1/sex from each litter.
  - voluntary exercise with rotating wheel - Day 21, to determine the total number of wheel rotation in 30 min.
  - righting, pupillary, pinna, cornea. Preyer (an auditory test), and vision reflex - Day 21;
  - open-field for mood behavior - week 5;
  - nultiple water T-maze test for learning ability - Week 7;
  - shuttle box test for conditioned avoidance responeses - Week 9.
- F_1 Reproductivity Test - Week 10, 2/sex from each dam. Males were sacrificed at the end of mating period, and the weights of testes and epididymis were determined. Testes, epididymis, prostate, scrotum, and abnormal parts were preserved in 10% formalin. The confirmed copulated females were housed individually. The following observation were carried out:
  - body weight - GD 0, 4, 7, 11, 14, 17, and 20;
  - C-section - GD-21, all F_1 females; ½ F_2 fetuses were fixed in Bouin's solution and the other ½ were preseved in 70% alcohol.

Results:

Effects on the F_0 Dams:

- Mortality & Clinical Signs - A total of 3 deaths occurred. Two ♀ at 400 mg/kg died during the treatment period, GD 13 & 17, respectively and one (1 @ 10 mg/kg) died on LD 15. One each from 50, 250 and 400 mg/kg groups were sacrificed on LD 1 after all the offspring were dead due to insufficient lactation. Salivation immediately after dosing was seen during the treatment for the animals at ≥250 mg/kg.
- Body Weight & Food Consumption - High-dose females had lower mean body weight (↓4-9%) from GD 9→21. A significant ↓ in weight gains (↓17% and 48%, respectively) during GD 7-21 accompanied by a ↓ food intake (6-22% and 14-25%, respectively) was observed in ♀ at 250 and 400 mg/kg. A slight but not statistical significant lower (8-12%) in food consumption during LD 4→21 was noted in the high-dose females.
- Reproductive Parameters - No significant differences in Nº of corpora lutea, Nº of implantations, Nº of resorbed/dead fetuses, and Nº of live fetuses were observed. A decrease in fetal body weight (♂ & ♀) was observed in dams at 250 & 400 mg/kg. An increase in gestation length (22.2 vs 21.6 days) was observed for dams at 250 & 400 mg/kg. The following table shows mean (±SD) reproductive indices for each group.

Reproductive Indices		Dose (mg/kg/day)				
		Vehicle Control	10	50	250	400
Nº of Corpora Lutea		16.4 ±1.6	16.1±1.5	16.5±1.6	16.5±1.9	16.5±1.9
Nº of Implantation Sites		15.6±1.1	15.2±1.8	14.9±2.3	14.7±3.4	15.4±2.7
Nº of Live Fetuses		15.1±1.0	14.7±1.9	14.4±2.3	14.1±3.2	14.6±2.8
Nº of Dead or Resorbed Fetuses		10 (3.0%)	11 (3.3%)	10 (3.2%)	15 (4.2%)	17 (5.0%)
Nº of Early Resorption		10	9	10	15	15
Nº of Late Resorption		0	2	0	0	2
Placental Weight (g)		0.5±0.06	0.50±0.06	0.50±0.05	0.49±0.08	0.42±0.05**
Fetal Weight (g)	♂	5.32±0.2	5.46±0.23	5.43±0.25	5.09±0.41**	4.54±0.43**
	♀	5.10±0.20	5.15±0.31	5.15±0.28	4.80±0.34**	4.31±0.36**
Gestation Length (Day)		21.5±0.5	21.9±0.3	22.0±0.4	22.2±0.4**	22.2±0.4**
Live Born		13.6±1.0	15.5±1.1	13.8±4.6	15.1±3.0	12.0±4.5
Nº of Still Born		4 (2.9%)	1 (0.6%)	2 (1.3%)	7 (4%)	4 (2.8%)
Live Birth Index* (%)		94.4	95.0	92.7	82.2	85.7

Significantly different from control value: **p<0.01. * Live Birth Index = (Nº of live born/Nº of implantation) x 100

Insufficient lactation due to under development of the mammary glands and nipples was found in one dam from each of 50, 250, & 400 mg/kg groups.

- Pathology - No significant findings were treatment related in F_0 dams sacrificed at weaning.

Effects on the F_1:

- Mortality & General Condition - The mean Nº of offspring/dam (9.6 vs 13.5) and 4-day survival rate (80.3% vs 99.3%) was significantly less in the 400 mg/kg group as shown in the following table. The weaning rate and maturity rate were not affected. External malformations were found in the offspring born to dams at 250 (one with absence of a tail) & 400 (2 with short tails) mg/kg.

Dose (mg/kg)		Nº of Dams	Day 0	Day 4	Day 4 Survival[a] (%)	Day 4	Day 21	Day 21 Weaning Index[b] (%)	Day 21	Day 70	Day 70 Survival[c] (%)
			Nº of Live Offspring			Nº of Live Offspring			Nº of Live Offspring		
0	Total Nº	10	136	135	99.3	80	79	98.8	58	58	100.0
	Mean±SD		13.6±1.9	13.5±1.9		8.0±0.0	7.9±0.3		5.8±0.4	5.8±0.4	
10	Total Nº	11	171	168	98.2	88	79	89.8	60	60	100.0
	Mean±SD		15.5±1.1**	15.3±1.6*		8.0±0.0	7.2±2.4		6.0±0.0	6.0±0.0	
50	Total Nº	11	153	144	94.1	80	78	97.5	60	60	100.0
	Mean±SD		13.9±4.6	13.1±4.8		8.0±0.0	7.8±0.4		6.0±0.0	6.0±0.0	
250	Total Nº	11	166	151	91.0	80	75	93.8	58	59	100.0
	Mean±SD		15.1±3.0	13.7±6.1		8.0±0.0	7.5±1.1		5.8±0.3	5.9±0.3	
400	Total Nº	11	132	106	80.3	69	66	95.7	52	50	96.2
	Mean±SD		12.0±4.5	9.6±5.4*		6.9±2.0	6.5±2.2		5.2±1.8	5.0±2.0	

[a] (Nº of live offspring at day 4/Nº of live born offspring at day 0) x 100.
[b] (Nºof live offspring at day 21/Nº of live offspring at day 4) x 100.
[c] (Nº of live offspring at day 70/Nº of live offspring at day 21) x 100.
* p≤0.05; ** P≤0.01 (Significant difference from control).

- Body Weight - A significantly lower mean body weight (↓5-15%) was noted in F_1 ♂ of the 400 mg/kg group from Days 0→70 postnatal. F_1 ♀ of high-dose group also had slightly lower mean body weight during PN 0→11 (↓5-7%) and 21→42 (↓5-8%).
- Neonatal Development of F_1- Higher numbers of F_1 from 10, 50 and 250 mg/kg groups (32, 33 and 29% vs 11.3% in controls) had eruption of lower incisor on Day 11 examination. Higher ratios of F_1 from 250 & 400 mg/kg groups also had eyelid separation (32-38% vs 19% in controls) on postnatal Days 14. No significant differences in the developmental parameters were identified during the second examination.
- Volunteer Motor, Reflex and Behavior - No significant findings in any parameter tested were drug-related.
- Reproductive Performance of F_1 - No significant differences in the copulation, fertility and pregnancy rates were seen. Female fetuses of F_1 born to dams (F_0) at 250 mg/kg had significantly less body weight. External examination of F_2 showed a single case of omphalocele in one fetus from the 250 mg/kg group.
- Pathology - Distention of the renal pelvis was the major gross finding with the incidence 15, 5, 25, 15, and 37.5% for ♂ and 0, 5, 0, 15, and 0% for ♀ in the 0, 10, 50, 250 and 400 mg/kg groups, respectively.

Effects on the Live F_1 Fetuses:

- Fetal Parameters - The results of examinations of the internal organs and skeletons of the live fetuses obtained by C-section are shown in the following table.

Parameters		Dose (mg/kg)				
		0	10	50	250	400
Visceral Examination						
Nº of Fetuses Examined		155	159	148	164	155
Nº of Fetuses with Abnormality		9 (6%)	11 (7%)	8 (5%)	8 (5%)	25* (16%)
Thymic Remnant in the Neck		3 (2%)	1	1	5 (3%)	16** (10%)
Interventricular Septal Defect		0	1	1	2 (1.2%)	6* (4%)
Enlarge of Auricle		0	0	0	0	1
Dilation of Renal Pelvis/Ureter		1	1	1	0	4
Skeletal Examination						
Nº of Fetuses Examined		163	163	155	173	163
Nº of Fetuses with Abnormality		0	0	0	0	0
Nº of Fetuses with Variations		22 (13.5%)	14 (8.6%)	23 (14.8%)	56** (32.4%)	38 (23.3%)
Wavy Rib		0	0	0	5 (2.9%)	7* (4.3%)
Splitting of Thoracic Vertebral Body		0	0	1	3 (1.7%)	6* (3.7%)
Nº of Ossified Sternebrae	1st-4th	163	163	155	173	163
	5th	153 (93.9%)	152 (93.3%)	143 (92.3%)	129** (74.6%)	85** (52.1%)
	6th	163 (100%)	162 ((99.4%)	154 (99.4%)	159** (91.9%)	117** (71.8%)
Nº of Ossified Metacarpus	Right	4.00	4.0	4.00	4.00	3.98
	Left	4.00	4.0	4.00	4.00	3.98
Nº of Ossified Metatarsus	Right	4.82	4.80	4.75	4.29**	4.07**
	Left	4.81	4.81	4.75	4.29**	4.07**
Nº of Ossified Sacral and Caudal Vertebrae		10.25	10.27	10.22	9.66*	9.11**

* $p \leq 0.05$; ** $p \leq 0.01$ (significant difference from control).

Therefore, the lowest no-observable-adverse-effect-level (NOAEL) for parental, reproductive, developmental and neonatal (perinatal and postnatal) toxicities in the present Segment I-II study were 50, 50, 50 and 50 mg/kg/day, respectively.

3.4.2.2. BMY-26517 (BLX): Teratology Study in Rabbits. (SR2121)(Vol. 1.28, p 93)

Teratogenicity of TBX in Rabbits. Jpn Pharmacol Ther 1990; 18: 1003-1015. (SR2121-P)(Vol. 1.28, p 163)

Report Nº: SR2121 & SR2121-P
Study Nº: R-071
Study Aims: To determine the possible teratogenic effects of TBX in rabbits following repeated oral dosing.
Compound: Pemirolast Potassium (TBX) (Lot Nº M-06) powder, dissolved in H_2O
Dose & Route: 0, 5, 10, 50 and 150 mg/kg/day, 0.5 ml/100 g po by gavage
Dosing Duration: 13 days (GD 6→18)
Animal: New Zealand white rabbits, ~6 months of age, weighing 3.30-4.37 kg, 18 mated ♀/group
Compliance with GLP/QAU: Yes
Study Period: 6/1/1984 - 4/5/1985
Dosing Date: 3/7/1985 - 3/26/1985
Study Site:
Study Designs: Groups of rabbits were dose with various of dosages of TBX by oral gavage from Gestation Days 7 to 17 as shown in the following table.

Group	Dose (mg/kg/day)	Dosing Volume (ml/kg)	Dosing Duration	Nº of Animals/Group
Control	0	5	Gestation Day 6→18	18 mated ♀
Low Dose	5			
Mid-Dose	10			
Mid-High	50			
High Dose	150			

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day.
- Body Weight - Gestation Days (GD) 0, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28.
- Food Consumption - GD 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28.
- C-Section - GD 28. Ovaries and uterus were removed and examined. The following reproductive performance fetal parameters were recorded. The heart, lungs, liver, kidneys, spleen, and ovaries were removed from dams, weighted, and preserved in 10% formalin.

  Examination of Dams
  - Nº of corpora leutea;
  - Nº of implants;
  - placental weight;
  - Nº of viable fetuses; and
  - Nº of dead and resorbed fetuses.

  Examination of Fetuses
  - external exmaination;
  - sex;
  - body weight; and
  - viseral (1/2 of fetuses) and skeletal (1/2 of fetuses) examinations.

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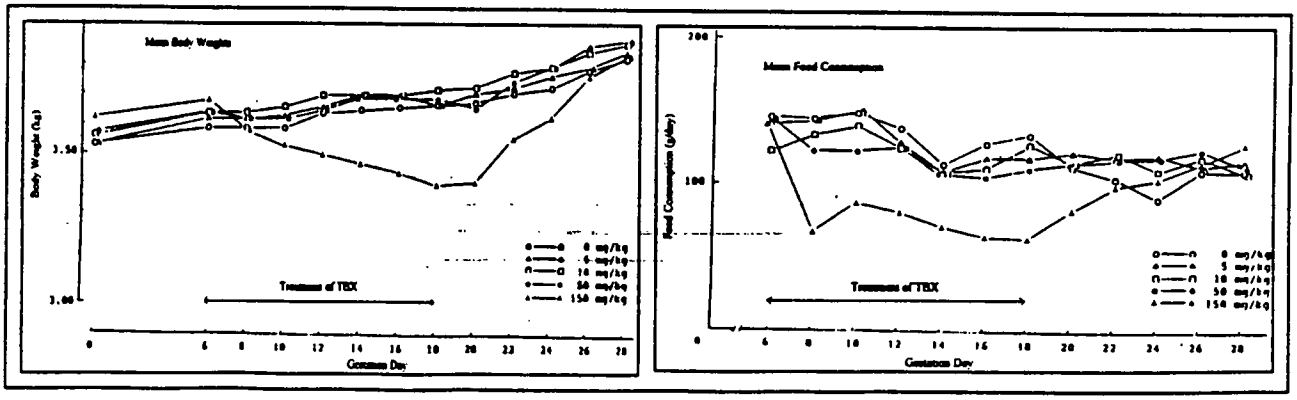
Results:

- General Signs and Mortality - Two in the 5 mg/kg group died on GD 18 and 19, respectively due to dosing error. One @ 10 mg/kg had hemorrhage in the vagina on GD 24. One @ 50 mg/kg had hematouria on GD 0→6 prior to TBX treatment. One high-dose animal showed increased respiration rate on GD 13, 14, and 17→28. Abortions were noted in 7 high-dose animals and 6/7 of these animals showed vaginal bleeding. One @ 25 mg/kg had premature delivery.
- Body Weight and Food Consumption - Weight loss (left panel) with reduce food intake (right panel) was noted in ♀ @ 150 mg/kg during the treatment (GD 6→18) as in the following two figures.



- Reproductive and Fetal Parameters - No statistically significant differences were noted in the mean Nº of corpora lutea, mean Nº of implantations, mean live or dead fetuses, placental and fetal body weights. However, slight increases in the Nº of total dead fetuses and the ratio Nº of total fetal deaths/Nº of Implantations were noted in all TBX-treated groups. The major findings for each group during external, visceral and skeletal examinations are presented in the following table.

Parameters		Dose (mg/kg)				
		0	5	10	50	150
Nº of Dams Examined		16	14	16	18	10
Nº of Corpora Lutea	Total	177	160	190	202	111
	(Mean±SD)	11.1 ± 1.6	12.01 ± 2 .2	11.91 ± 1 .4	11.2 ± 2.5	11.1 ± 2.6
Nº of Implantations	Total	156	142	155	173	85
	(Mean±SD)	9.8 ± 11.6	10.1 ± 2.7	9.7 ± 2.4	9.6 ± 13.1	8.5 ± 12.5
Nº of Fetal Deaths	Early Death	5	13	5	14	10
	Late Death	2	3	8	5	1
	Total	7	16	13	19	11
Nº of Fetal Deaths/ Nº of Implantations (%)		4.5	11.3	8.4	11.0	12.9
Nº of Live Fetuses	Total	149	126	142	154	74
	(Mean±SD)	9.3 ± 2.0	8.0 ± 3.4	9.5 ± 2.3	9.1 ± 3.0	8.2 ± 2.2
Sex Ratio (♂/♀)		1.13 (79/70)	0.77 (55/71)	0.71 (59/83)	0.88 (72/82)	0.95 (36/38)
Body Weight (Mean±SD)(g)	♂	31.92 ± 5. 35	31.01 ± 5.65	31.16 ± 5.10	30.89 ± 5.83	33.40 ± 4.09
	♀	31.81 ± 4.74	29.93 ± 9.19	30.16 ± 5.10	29.58 ± 5.28	30.31 ± 3.35
Placental Weight (Mean±SD) (g)		3.48 ± 0.67	3.30 ± 0.83	3.34 ±0.72	3.18 ± 0.56	3.44 ± 0.54
External Malformation		1 (0.7%)[a]	1 (0.8%)[b]	0	0	0
VISCERAL EXAMINATION OF FETUSES						
Nº of Fetuses Examined		148	125	142	154	74
Nº of Fetuses with Abnormalities		3 (2.03%)	2 (1.6%)	3 (2.11%)	1 (0.65%)	4 (5.41%)
Supernumerary Right Coronary Orifice		3 (2.03%)	2 (1.60%)	0	0	2 (2.7%)
Persistent Truncus Arteriosus		0	1 (0.80%)	1 (0.7%)	0	0
Ventricular Septal Defect		1 (0.68%)	0	1 (0.7%)	1 (0.65%)	0
Thymic Remnant in the Neck		0	0	0	0	2 (2.7%)
Dilatation of the Renal Pelvis		0	1 (0.8%)	1 (0.7%)	0	0
Nº of Fetuses with Left Common Carotid Artery Rising from Aorta		28 (18 92%)	3 (2.4%)	14 (9.86%)	9 (5.84%)	3 (4.5%)

[a] Hydrocephaly, flexion contracture of the wrist joint, oligodactyly of the forelimbs, adhesion of the forelimbs to the abdominal skin, and absence of ungues.

[b] Excephaly, flexion contracture of the wrist join, and a bent tail.

Therefore, the lowest no-observable-adverse-effect-level (NOAEL) for parental, reproductive, and developmental toxicities in the present Segment II study were 50, 150 and 150 mg/kg/day, respectively.

3.4.3. PERI- AND POST-NATAL TOXICITY (SEGMENT III)

3.4.3.1. [redacted]-26517 (TBX): Peri- and Post-natal Reproductive Toxicity (Segment III) Study in Rats. (SR2109)(Vol. 1.28, p 199)

Peri- and Postnatal Study of TBX in Rats. Jpn Pharmacol Ther 1990; 18(3): 959-1001 (SR2109-P)(Vol. 1.28, p 00286)

Report Nº: SR2109 & SR2109-P
Study Nº: R-113
Study Aims: To determine the effects of TBX on gestation, parturition, and lactation in the dams and the development, survival, behavior and reproductive performance of the pups.
Compound: Pemirolast Potassium (TBX) (Lot Nº M-06) powder dissolved in H_2O
Dose & Route: 0, 10, 50, 250 and 400 mg/kg/day, 0.5 ml/100 g po by oral gavage from Gestation Day 17 through Lactation Day 21

Animals: 50♂ & 140♀ Crj:CD(SD) rats, ~12 weeks of age, weighing 379-451g for the ♂ and 225-283 g for the ♀, 24 mated ♀/group

Compliance with GLP/QAU: Yes

Study Site:

Study Date: 6/20/1986 (1st dosing) - 10/31/1986 (termination of the study)

Study Designs: Pregnant female rats were randomly assigned to 5 different groups and given various oral dose of TBX from as shown in the following table

Group	Dose (mg/kg/day)	Dosing Volume (ml/kg)	Dosing Duration	Nº of Animals/Group
Control	0	5	GD 17→LD 21	24♀
Low Dose	10			
Mid-Dose	50			
Mid-High	250			
High Dose	400			

The following observations were conducted.

- Clinical Signs and Mortality - 3x/day.
- Body Weight - Gestation Days (GD) 0, 7, 14, 17, 19, and 21; Lactation Days (LD) 0, 2, 4, 7, 11, 14, 17, and 21.
- Food Consumption - GD 1, 4, 7, 11, 14, 17, and 20; LD 1, 4, 7, 11, 14, 17, and 21.
- Neonatal Examination (Natural Delivery) - All dams were allowed to deliver naturally and allowed to nurse newborns for 21 days. The gestation period and live birth rate were recorded. On LD 22, all F_0 dams were sacrificed. The nursing ability was also evaluated. The heart, lung, liver, kidney, ovaries and spleen were weighted. The uterus was examined for the Nº of implantation traces, weighed, and preserved in 10% formalin. The following parameters were recorded for the newborns:
  - litter size, sex;
  - Nº of stillbirths;
  - external malformations; and
  - body weight - 2x/week to Post Natal Day (PND) 21, 1x/week to PND 70.
  - mortality - 1x/day up to PND 70.
- Differentiation Examination of Newborns - On PND 4, 4/sex newborns from each litter were randomly selected and remaining newborns were sacrificed. Four-day survival rate was calculated. The following parameters were examined for the development and differentiation of the newborns. When differentiation was noted 1st examination, no 2nd examination was attempted.
  - unfolding of the ear - PND 4 and 7;
  - hair growth - PND 7-11;
  - eruption of incisors - PND 11 and 14;
  - seperation of eyelids - PND 14 and 17;
  - decent of the testes - PND 21 and 28;
  - vaginal opening - PND 35 and 42.
- F_1 Behavior and Functional Tests - Three/sex from each litter were selected and weaned. The remaining (1/sex) animals were sacrificed and the brain, hearts, lungs, liver, kidneys, adrenal glands, spleen, and testes or ovaries were weighed and preserved in 10% formalin. The following tests were carried out in 1/sex from each litter.
  - voluntary exercise with rotating wheel - Day 21, to determine the total number of wheel rotation in 30 min.
  - righting, pupillary, pinna, cornea, Preyer (an auditory test), and vision reflex - Day 21;
  - open-field for mood behavior - week 5;

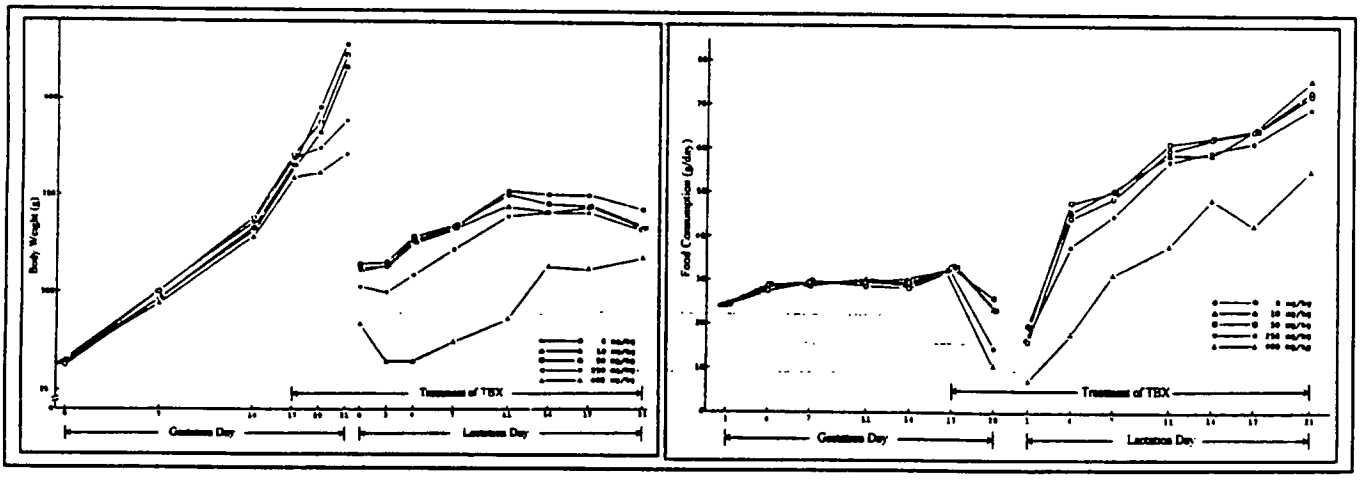
- nultiple water T-maze test for learning ability - Week 7;
- shuttle box test for conditioned avoidance responeses - Week 9.

- F_1 Reproductivity Test - Week 10, 2/sex from each dam. Males were sacrificed at the end of mating period, and the weights of testes and epididymis were determined. Testes, epididymis, prostate, scrotum, and abnormal parts were preserved in 10% formalin. The confirmed copulated females were housed individually. The following observation were carried out:
  - body weight - GD 0, 4, 8, 12, 16, and 21;
  - C-section - GD 21, all F_1 females; ½ F_2 fetuses were fixed in Bouin's solution and the other ½ were preseved in 70% alcohol.

Results:

Effects on the F_0 Dams:

- Mortality & Clinical Signs - No deaths and abnormal signs were observed in the groups at ≤50 mg/kg/day. A total of 10 animals (3 @ 250 mg/kg/day, one each on GD 21, 22 and 23; 7 @ 400 mg/kg/day, 5 on GD 22, one on GD 23 and one on LD 6) died during the experiment with general clinical signs of ↓ body temperature, prostrate, salivation and pale. At postmortem, splenic atrophy, adrenal enlargement and gastric lesions (red/dark spots in the glandular stomach) were noted.
- Body Weight & Food Consumption - A significant ↓ in mean body weight gains was seen in all treated animals during GD 17→21 (↓18%, ↓17%, ↓68, and ↓79% for 10, 50, 250, and 400 mg/kg, respectively). The mean body weight changes for each group during gestation and lactation periods depicted are illustrated in the following left figure. Yet, the animals at ≤50 mg/kg/day had normal weight gains during GD 19→21. The mean body weights of F_0 dams at 400 mg/kg/day was significantly lower ($p \leq 0.01$) than by 7-19% during lactation period (LD 0→21). Reduced food



consumption (↓9-59%) was seen in all treated animals during GD 17→20 as depicted in the above right figure. In addition, the dams at 400 mg/kg/day consumed significantly less food (22-60%) throughout the lactation period.

- Reproductive Performance - Significant ↓ in live births, ↓ birth rate and ↑ Nº of stillbirths were observed for the dams at 400 mg/kg/day as shown in the following table. Reduced birth rate was also observed for the dams at 250 mg/kg. The sex ratio of live offspring of the TBX-treated groups was similar to that of the control group.

Parameters		Dose (mg/kg)				
		0	10	50	250	400
Nº Pregnant ♀		22	23	21	24	23
Nº of ♀ Deliver Live Offspring		22	23	21	21	16
Delivery Index[a]		100	100	100	87.5	69.6*
Total Nº of Implantation (Mean ±SD)		358 (16.3±1.8)	360 (15.7±1.9)	349 (16.6±1.9)	326 (15.5±2.9)	251 (14.8±3.1)
Still Birth (%)[b]		22 (6.6%)	7 (2.1%)	4 (1.2%)*	5 (1.7%)	27 (12.1%)
Nº of Live Birth	Total (Mean ±SD)	310 (14.1±2.5)	334 (14.5±1.8)	323 (15.4±1.8)	290 (13.8±3.1)	196 (11.5±4.3*)
	♂ (Mean ±SD)	164 (7.5±2.4)	182 (7.9±2.4)	154 (7.3±2.2)	128 (6.1±2.5)	93 (5.5±3.2*)
	♀ (Mean ±SD)	146 (6.6±2.4)	152 (6.6±1.9)	169 (8.0±2.3)	162 (7.7±1.9)	103 (6.1±3.0)
Sex Ratio (♂/♀)		1.12	1.2	0.91	0.79	0.9
Live Birth Index[c]		86.6	92.8	92.6	89	78.1

[a] (Nº of females delivered live offspring/Nº of pregnant females) x 100; [b] [(Nº of stillborn offspring)/(Nº of stillborn + live born offspring)] x 100.; [c] (Nº of live born offspring/Nº of implantations) x 100; * $p<0.05$ (Significant difference from control).

- Nursing Performance - Incompetence of the nursing dams due to retarded development of the nipples/mammary glands or the poor physical condition was found in one at control, 2 @ 250 mg/kg/day, 11 @ 400 mg/kg/day. The offspring of these dams mostly died between LD 1→11.
- Necropsy Findings - The gross findings for the incompetent nursing dames included malformations of the nipples and mammary glands. Additionally, atrophy of the thymus and spleen, softening of the kidneys, and scattered spots on the glandular stomach were observed in these dams from 250 & 400 mg/kg/day groups. The macroscopic findings for the dams at weaning were: hydropic vesicles in the kidney (1 @ 10 and 1 @ 250 mg/kg), thymic atrophy (1 @ 250 & 1 @ 400 mg/kg), distended and thickening small intestine (1 @ 400 mg/kg), and white patches on the kidney (1 @ 400 mg/kg). A significant reduction in the absolute ovary weights was seen in dams at 250 (L: ↓12.4%; R: ↓6%) & 400 (L: ↓29%; R: ↓7%) mg/kg/day.

Effects on the F_1:

- Mortality - The survivals of F_1 born to dams at 250 & 400 mg/kg were much lower than offspring from the control group. The 4-day survivals of F_1 offspring are presented as follows:

Dose (mg/kg)	Nº of Dams	Nº of Live F_1		Survival Rate on Postnatal Day 4
		Postnatal Day 0	Postnatal Day 4	
0	22	310	284	91.6
10	23	334	326	97.6
50	21	323	314	97.2
250	21	290	239	82.4
400	16	196	65	33.2

- Body Weights - The mean body weights of ♂ & ♀ F_1 born to dams at 250 (♂: ↓5-10%; ♀:↓5-13%) & 400 (♂: ↓15-48%; ♀: ↓12-42%) mg/kg were significantly lower than the control offspring from postnatal Days 0→70.
- Development - A delay in incisor eruption and vaginal opening was observed in F_1 from 250 & 400 mg/kg groups. Delayed eyelid separation and descent of testis was also identified in F_1 from 400 mg/kg group.
- Necropsy Findings of F_1 ♀ at Weaning - Significantly ↓ absolute organ weights of kidney, spleen, adrenal, testes, ovaries, lungs, and heart were noted for the F_1 from 250 & 400 mg/kg groups as presented in the following table.

Dose (mg/kg)	Brain	Heart	Liver	Spleen	Kidney		Ovary	
					L	R	L	R
250	-	↓11%	↓11%	↓17%	↓14%	↓15%	↓10%	↓17%
400	↓11%	↓84%	↓23%	↓45%	↓30%	↓32%	↓34%	↓37%

- Reflex and Behavior in F_1 - There were no adverse effects on the volunteer motor activity, reflex and behavior in the F_1 attributable to the treatment of F_0 with TBX. Necropsy was performed on these F_1 at the end of testing (postnatal Day 63). Gross findings were distention of the renal pelvis (3♂ @ 0, 2♀ at 10 mg/kg), and yellow nodes in the abdominal cavity (1♂ @ 50 mg/kg).
- Reproductive Functions in F_1 - Lower fertility index[2] (71.4% vs 92.7% in controls) and pregnancy index[3] (75% vs 92.7% in the controls) for the F_1 born to 400 mg/kg F_0 were noted. In addition, significantly lower mean body weights (250 mg/kg: ↓4-5%; 400 mg/kg: ↓13-16%) with reduced weight gains (250 mg/kg: ↓5%; 400 mg/kg: ↓20%) were observed in the F_1 dams in ≥250 mg/kg groups during Gestation Days 0→21. Significant ↓ in the Nº of corpora lutea, and Nº of implantation, Nº of live fetuses were found in F_1 females born to F_0 treated with TBX at 250 or 400 mg/kg.

Parameters		Dose (mg/kg)				
		0	10	50	250	400
Nº of F_1 Dams Examined		38	43	41	33	6
Nº of Corpora Lutea (Mean±SD)		667 (17.6 ± 2.0)	706 (16.4 ± 2.5*)	689 (16.8 ± 1.9)	512 (15.5 ± 3.0**)	85 (14.2 ± 1.0**)
Nº of Implantations (Mean±SD)		614 (16.2 ± 1.7)	641 (14.9 ± 4.0)	643 (15.7 ± 2.2)	458 (13.9 ± 3.6**)	70 (11.7 ± 4.0**)
Nº of Resorbed or Dead Fetuses	Early	42	35	45	26	10
	Late	1	1	2	1	1
	Total	43 (7.0%)	36 (5.6%)	47 (7.3%)	27 (5.9%)	11 (15.7%)
Nº of Live Fetuses (Mean±SD)		571 (15.0 ± 1.9)	605 (14.1 ± 4.2)	596 (14.5 ± 2.3)	431 (13.1 ±3.8**)	59 (9.8 ± 4.4*)
Sex Ratio (♂/♀)		0.94 (276/295)	0.97 (298/307)	1.02 (301/295)	0.99 (214/217)	0.84 (27/32)
Body Weight (Mean±SD) (g)	♂	5.12 ± 0.23	5.24 ± 0.35	5.17 ± 0.32	5.23 ± 0.41	5.42 ± 0.40
	♀	4.88 ± 0.25	4.97 ± 0.33	4.89 ± 0.28	4.96 ± 0.46	5.08 ± 0.46
Placental Weight (Mean±SD) (g)		0.49 ± 0.07	0.51 ± 0.09	0.49 ± 0.06	0.51 ± 0.08	0.66 ± 0.25
External Malformation		2 (0.4%)[a]	2 (0.3%)[b]	2 (0.3)[c]	0	0

[a] Agnathia (1) and exencephaly + myeloschisis + exophthalmia (L) + omphalocele (1).
[b] Vestigial tail (1) and adactyl forelimbs (1).
[c] exencephaly with cleft lip (1) and vestigial tail (1).

Necropsy findings of F_1 involved in the reproductive function study were dilation of renal pelvis (3♂ & 5♀ @ 0, 4♂ & 3♀ @ 10, 2 @ 50, 1 @ 250 mg/kg), enlargement of testis (1 @ 50 mg/kg), and atrophy of testis and epididymis (3 @ 250 mg/kg). Reduced absolute testis (↓9-12%) and epididymis (↓~11%) weights were noted for the ♂ F_1 born to F_0 treated with TBX ≥250 mg/kg. Therefore, the lowest no-observable-adverse-effect-level (NOAEL) for parental, reproductive and neonatal (perinatal and postnatal) toxicities in the present study were 50, 50 and 50 mg/kg/day, respectively.

3.5. GENOTOXICITY

3.5.1.1. [redacted]26517 (TBX): Reverse Mutation Assay with Bacteria (Translation). (SR2120)(Vol. 1.29, p 1)

Report Nº: SR2120
Study Nº: 85-009
Study Aims: To determine the mutagenic potential of TBX to induce reverse mutation in Ames assay.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O: 10, 50, 100, 500, 1000, & 5000 μg/plate

[2] Fertility Index = (Nº of impregnated ♂/Nº of copulated ♂) x 100
[3] Pregnancy Index = (Nº of pregnant ♀/Nº of copulated ♀) x 100

(+) Control: 2-Aminoanthracene(2AA); N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG); 1,3-Propanediamine-N-(2-chloroethyl)-N'-6-chloro-2-methoxy-9-acridinyl) dihydrochloride (ICR-191); 2-Nitrofluorene (2NF)

(-) Control: Dist. H_2O; DMSO

S9: prepared from the liver of phenobarbital and 5, 6-benzoflavone induced 7-week old Sprague-Dawley ♂ rats.

Bacteria: *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537 and TA1538; *Escherichia coli* strain WP2 uvr A

Bacteria	Strain	Dose (μg/plate)	
		- S9	+ S9
Salmonella typhimurium	TA 100	ENNG: 5, 10, 15	2AA: 1, 2, 4
	TA1535	ENNG:10, 20, 30	2 AA: 2, 4, 8
	TA98	2 NF: 1, 2, 4	2AA: 0.5, 1, 2
	T1537	ICR-191: 0.1, 0.2, 0.4	2 AA: 2, 4, 8
	TA1538	2NF: 1, 2, 4	2AA: 0.5, 1, 2
Escherichia coli	WP2 uvr A	ENNG: 1, 2, 4	2AA: 10, 20, 40

Incubation Time: 37°C for 44-45 hr

Compliance with GLP/QAU: Yes

Study Date: 10/4/1985 - 11/25/1985

Study Site:

Results: TBX at the concentrations of 10, 50, 100, 500, 1000, or 5000 μg/plate did not increase the numbers of revertant of *Salmonella typhimurium* (strain TA98, TA100, TA1535, TA1547 and TA1538) and *Escherichia coli* (strain WP2 uvr A). **Therefore, TBX was not mutagenic under the present testing condition.**

3.5.1.2. Reverse Mutation Test of a TBX (BW-26517) Metabolite (TBX-01) Using Bacteria. (SR2152)(Vol. 1.29, p 31)

Report Nº: SR2152

Study Aims: To determine the mutagenic potential of TBX-01, a dominant TBX metabolite present in the urine excretion, to induce reverse mutation in Ames assay.

Compound: TBX-01 in DMSO: 10, 50, 100, 500, 1000, & 5000 μg/plate

(+) Control: 2-Aminoanthracene(2AA); N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG); 1,3-Propanediamine-N-(2-chloroethyl)-N'-6-chloro-2-methoxy-9-acridinyl) dihydrochloride (ICR-191); 2-Nitrofluorene (2NF)

(-) Control: Dist. H_2O; DMSO

S9: prepared from the phenobarbital and 5, 6-benzoblavone induced rat liver.

Bacteria: *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537 and TA1538; *Escherichia coli* strain WP2 uvr A

Incubation Time: 37°C for 2 days

Bacteria	Strain	Dose (μg/plate)	
		-S9	+S9
Salmonella typhimurium	TA 100	ENNG: 5, 10, 15	2AA: 1, 2, 4
	TA1535	ENNG:10, 20, 30	2 AA: 2, 4, 8
	TA98	2 NF: 1, 2, 4	2AA: 0.5, 1, 2
	T1537	ICR-191: 0.1, 0.2, 0.4	2 AA: 2, 4, 8
	TA1538	2NF: 1, 2, 4	2AA: 0.5, 1, 2
Escherichia coli	WP2 uvr A	ENNG: 1, 2, 4	2AA: 10, 20, 40

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Compliance with GLP/QAU: Yes

Study Date: 2/21/1989 - 4/26/1989
Study Site: [redacted]

Results: TBX-01, the hydroxyl metabolite of TBX, at the concentrations of 10, 50, 100, 500, 1000, or 5000 μg/plate did not increase the numbers of revertant of *Salmonella typhimurium* (strain TA98, TA100, TA1535, TA1547 and TA1538) and *Escherichia coli* (strain WP2 uvr A). **Therefore, TBX-01 were not mutagenic under the present testing condition.**

3.5.1.3 [redacted]-26517-31: Ames Microbial Mutagenicity Assay. (SR2151 (Vol. 1.29, p 43)

Report Nº: SR2151
Study Nº: 85077
Study Aims: To determine the mutagenic potential of TBX of to induce reverse mutation in Ames assay.
Compound: [redacted]26517-31 (Lot Nº M-06) dissolved in distilled H_2O: 100, 500, 1000, 2500, & 5000 μg/plate
(+) Control: 2-Aminoanthracene(2-AA), 0.25 and 0.5 μg/plate; 9-Aminoacridine (9-AA), 50 and 25 μg/plate; NaN_3, 2.5 and 5.0 μg/plate; 2-Nitrofluorene (2-NF), 0.5 and 2.0 μg/plate
(-) Control: Dist. H_2O; DMSO, 3.7%
S9: prepared from the liver of Aroclor 1254 induced Sprague-Dawley ♂ rats.
Bacteria: *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537 and TA1538
Incubation Time: 37°C for 42-68 hr
Compliance with GLP/QAU: Yes
Study Date: 8/6/1985 - 12/11/1985
Study Site: [redacted]

Bacteria	Strain	Dose (μg/plate)	
		- S9	+ S9
Salmonella typhimurium	TA 100	NaN_3: 2.5, 5.0	-
	TA 1535	NaN_3: 2.5, 5.0	-
	TA 98	2-NF: 0.5, 1.0	-
	TA 1537	9-AA: 25.0, 50.0	-
	TA 1538	2-AA: 0.25, 0.5	2-AA: 0.25, 0.5

Results: -26517-31 at the concentrations of 100, 500, 1000, 2500 or 5000 μg/plate did not increase the numbers of revertant of *Salmonella typhimurium* (strain TA98, TA100, TA1535, TA1547 and TA1538). **The positive control 2-AA for TA 1538, did not cause an increase in the number of revertant under the condition without metabolic activation. In addition, under the condition without S9, no positive controls were included for strain TA 98, 100, 1535, and 1537. Therefore, no conclusions could be properly drawn from the present report as either the positive control was not working or no appropriate positive controls were included .**

3.5.1.4. -26517-31: CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay. (SR2157)(Vol. 1.29, p 94)

Report Nº: SR2157
Study Nº: 90027
Study Aims: To determine the mutagenic potential of pemirolast in the Chinese hamster ovary/HPRT forward gene mutation assay.

Compound: [redacted]26517-31 (Lot Nº C89G139) dissolved in distilled H_2O: 250, 500, 750, 1000 μg/ml
(+) Control: -S9: Ethyl Methane Sulfonate (EMS), 200 μg/ml; +S9: Benzoapyrene, 2 μg/ml
(-) Control: Dist. H_2O, 20 μl/ml
S9 (2%): prepared from the liver of Aroclor 1254 induced Sprague-Dawley ♂ rats.
Indicator Cells: CHO-K1-BR-4 cells
Incubation Time: 37°C for 5 hr
Compliance with GLP/QAU: Yes
Study Date: 4/30/1990 - 11/19/1990
Study Site: [redacted]

Results: [redacted]26517-31, up to 1000 μg/ml, was not mutagenic to CHO cells in the presence or absence of metabolic activation mix S9 under the current testing condition.

3.5.1.5. BW-26517-31: Primary Rat Hepatocyte DNA Repair Assay. (SR2156)(Vol. 1.29, p 124)

Report Nº: SR2156
Study Nº: 86056
Study Aims: To determine the genotoxic potential of pemirolast in the primary rat hepatocytes to induce DNA repair by measurement of unscheduled DNA synthesis (UDS).
Compound: [redacted]26517-31 (Lot Nº S85J023) dissolved in distilled H_2O: 1.0, 3, 10, 25, 50, 100, 250, 500, 750, and 1000 μg/ml
(+) Control: 2-Aminofluorene (2-AF), 0.1, 0.5 μg/ml
(-) Control: DMSO, 0.5%; Dist. H_2O, 2%; Fluorene, 3 and 10 μg/ml
Indicator Cells: primary rat hepatocytes from a ♂ Fischer 344 rat
Exposure Time: 37°C for 19 hr
Method: Autoradiography by pulsing cells with ^{3}H-thymidine, 10 μCi/ml
Compliance with GLP/QAU: Yes
Study Date: 5/23/1986 - 11/9/1988
Study Site: [redacted]

Results: Data showed that [redacted]26517-31, up to 1000 μg/ml, did not increase unscheduled DNA synthesis.

3.5.1.6. Chromosomal Aberration Test with Chinese Hamster Lung Fibroblasts. (SR2315)(Vol. 1.29, p 166)

Report Nº: SR2315
Study Nº: 86-004, MADI-H-21372
Study Aims: To evaluate mutagenic potential of TBX to induce chromosomal aberration in Chinese hamster lung cells.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O:
-S9: 94, 188, 375, & 750 μg/ml
+S9: 375, 750, 1500 & 3000 μg/ml
(+) Control:
-S9: Mitomycin (MMC), 0.05 & 0.1 μg/ml
+S9: Dimethylnitrosamine (DMN), 500 & 1000 μg/ml
(-) Control: Saline; DMSO
S9: Prepared from the phenobarbital and 5, 6-benzoblavone induced rat liver.

Dose & Route: 1030-2745 mg/kg po; 410-800 mg/kg sc, 139-415 mg/kg iv
Indicator Cells: CHL/IU derived from the lungs of Chinese hamster
Exposure Time: -S9: 37°C for 2 days; +S9: 37°C for 6 hr
Compliance with GLP/QAU: Yes
Study Date: 8/21/1986 - 11/13/1986
Study Site:

Results: TBX did not increase incidences of cells with structural abnormality and polyploid cells under the conditions with or without S9 mix. **Therefore, TBX was not clastogenic in the present assay.**

3.5.1.7. Micronucleus Test in Rats. (SR2155)(Vol. 1.29, p 196)

Report Nº: SR2155
Study Aims: To assess clastogenic potential of TBX in the rat bone marrow micronucleus test.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O; Cyclophosphamide (CP) in saline
Dose & Route:

Single-Dose Experiment		5 Repeated-Dose Experiment	
Compound	Dose (mg/day)	Compound	Dose (mg/day)
Control	0	Control	0 for 5 Days
TBX	50	TBX	25 for 5 Days
	100		50 for 5 Days
	200		100 for 5 Days
	400		200 for 5 Days
Cyclophosphamide	20	Cyclophosphamide	10 for 5 Days

Animal: 72 ♂ Crj:CD rats, ~6 weeks of age, weighing 226-245 g, 6/group
Compliance with GLP/QAU: Not Indicated
Study Date: 11/09/1988 - 3/29/1989
Study Site:

Results: Data from single day or 5-day treatment with TBX or positive control cyclophosphamide are presented in the following table.

Single-Dose (mg/kg) Experiment				5 Repeated-Dose (mg/kg/day) Experiment			
Compound	Dose	PCE %	MNPCE %	Compound	Dose	PCE* %	MNPCE* %
Control	0	61.5 ± 5.43	0.12 ± 0.12	Control	0	59.5 ± 5.05	0.13 ± 0.10
TBX	50	53.7 ± 14.6	0.05 ± 0.08	TBX	25	48.4 ± 12.77	0.07 ±0.08
	100	48.9 ± 15.43	0.12 ± 0.08		50	58.5 ± 7.45	0.02 ± 0.04
	200	56.6 ± 7.60	0.15 ±0.12		100	48.9 ± 9.12	0.13 ± 0.10
	400	57.5 ± 12.45	0.10 ± 0.11		200	51.9 ± 7.65	0.05 ± 0.05
CP	20	50.1 ± 6.74	2.48 ± 0.42*	CP	10	51.9 ± 8.31	3.40 ± 0.89*

P<0.05: Significant from control; Kastenbaum and Bowman's method.
* Percent of polychromatic erythrocytes;
* Percent of micronucleated polychromatic erythrocytes.

The frequencies of micronucleated polychromatic red cells were not increased in the animal treated with various levels of TBX for one day or 5 days. **Therefore, TBX was not clastogenic in the micronucleus assay.**

3.5.1.8. BW-26517-31: In Vivo Cytogenetic Assay in Rats. (SR2145)(Vol. 1.29, p 209)

Report Nº: SR2145

Study Nº: 86032
Study Aims: To assess clastogenic potential of TBX to induce chromosomal aberrations in the rat bone marrow cells.
Compound: BW-26517-31 (Lot Nº S85J023) dissolved in H_2O, 25 mg/ml; Cyclophosphamide (CP) in distilled H_2O, 2.8 mg/ml
Vehicle Control: H_2O for injection
Dose & Route: 250 mg/kg for TBX and 28 mg/kg for CP ip single dose

Compound	Dose (mg/kg)	Dose Volume (ml/kg)	Nº Animals Sacrifice		
			6 hr	24 hr	48 hr
Control (H_2O)	0	10	5/sex	5/sex	5/sex
TBX	250	10	5/sex	5/sex	5/sex
Cyclophosphamide	28	10		5/sex	

Animal: Sprague-Dawley rats, Crl:CD9SD)BR, ~8 weeks of age, weighing 160-184 g, 65/sex/group/time point
Compliance with GLP/QAU: Yes
Treatment Date: 9/17/1986
Study Site: [redacted]

Results: Treatment of TBX at a dose of 250 mg/kg did not cause an increase in the incidence of chromosomal aberrations in rat bone marrow cells at 6, 24, or 48 hr post ip administration

3.6. SPECIAL TOXICITY

3.6.1.1. [redacted]26517 (BLX): Toxicity Study in Beagle Dogs - Effects on the Visual Organs. (SR2153)(Vol. 1.17, p 1)

Report Nº: SR2153
Study Nº: 83-002
Study Aims: To evaluate the effects of TBX on the visual system.
Compound: Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O
Dose & Route: iv - 0.5, 10, and 200 mg/0.1-2 ml/kg, single dose.
po - 10, 50, 300 mg/2.5 ml/kg po for 21 days.
Vehicle Control: 3% KCl, 3 ml/kg for the iv route and distilled H_2O for the po route
Doing Duration: single dose for iv and 21 days for po
Animal: Mongrel dogs for the preliminary dose-finding study; beagles, 3/group for the main study
Compliance with GLP/QAU: Not Indicated
Study Date: 01/10/1984 - 4/23/1985
Study Site: [redacted]

Study Designs: The following parameters were monitored.

- Clinical Signs - 1x/day;
- Body Weight - Pre-R and Weeks 1, 2, and 3.
- Hematology and Clinical Chemistry - Weeks 1, 2, and 3.
- Visual Examination and Palpation of the Eyes - iv: Pre-R, 60 and 120 min post dosing; po: 1x/day before dosing.
- Ophthalmofundoscopic Study - iv: Pre-R, 60 and 120 min post dosing; po: Weeks 1, 2, and 3, 1x Pre-R and after dosing.

- Electroretinography (ERG) - iv: Pre-R, 15, 30, 45, 60 and 120 min post dosing; po: Weeks 1, 2, and 3, 1x before dosing.
- Necropsy -
  Organ Weights: The following organs were weighed: heart, lungs, liver, spleen, kidneys, suprarenal glands, testes, ovaries, and eyeballs.
  Visual organs from each dog at the end of each study and the liver and the kidney from oral study groups were preserved in 10% buffered formalin. Microscopic examinations of visual organs (the cornea, lens, iris, ciliary body, retina, choroid, sclera, and optic papilla) and the liver and the kidney from oral study groups were performed.

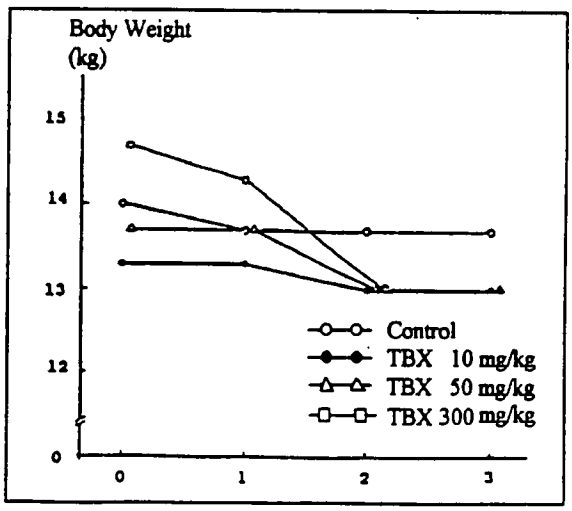
Results:

IV (Single Dose) Administration:

- Clinical Signs & Mortality - For dogs at 200 mg/kg, 3/3 showed salivation, 2/3 had abnormal gait, one showed pinhole pupils 24 hr post administration and 2/3 dogs died during the test.
- Visual Examination and Palpation - One dog at 200 mg/kg had pinhole pupils 24 hr post dosing. No other effects were noted.
- Ophthalmofundoscopic Examination - No abnormalities were identified attributable to the treatment.
- Electroretinography (ERG) - The kinetic changes in ERG before and after dosing were recorded One dog at 0.5 mg/kg had a slight decrease in A-a and A-b waves in ERG measured 120 min post dosing. Marked decreases in wave A-a and A-b were seen in 2/3 dogs at 10 mg/kg at 120-180 min post administration. All (3/3) animals @ 200 mg/kg had markedly decreased waves A-a and A-b at 15 min post dosing **an indicative of abnormal photoreceptor cells and defective retinal neuron functions**. Two animals at 200 mg/kg died during the test. The survival one had a normal ERG at 24 hr post dosing.
- Necropsy - ~~Severe post mortem changes were seen in one dog~~ @ 200 mg/kg that died during the test. Ulcers and red spots in the stomach, red spots in the gall bladder, red spots in the entire GI tract were observed in one dog at 200 mg/kg that died one day post dosing.
  Histopathological Examination: Congestion and hemorrhage in the iris, and a slight cellular infiltration in the iris and ciliary body were found in one dog at 200 mg/kg that died during test. A slight cellular infiltration in the space between the iris and the cornea (1/3) and a partial loosening of corneal epithelium (2/3) were identified in dogs @ 0.5 mg/kg. No abnormalities were noted in the dogs @ 10 mg/kg.

Oral Repeated Dose Administration:

- Clinical Signs & Mortality - Vomiting, and soft/bloody stools were the major clinical complaints for the dogs at 300 mg/kg. All three dogs in this group died before the completion of the study.
- Body Weights - A slight loss (no actual data were presented in the report) in the body weight was observed in dogs at 50 and 300 mg/kg as illustrated in the right figure.
- Visual Examination and Palpation - One dog @ had severe pinhole pupils on day 14, hemorrhage in the eye chambers of both eyes and reddening of the conjunctiva of both eyes on Day 15, and died on Day 16.



- Ophthalmofundoscopic Examination - The dog @ 300 mg/kg that had pinhole pupils was not examined at Week 2. All examined animals did not show any abnormality.
- Electroretinography (ERG) - No abnormalities were noted for dogs in the 10 and 50 mg/kg groups. In the high dose group (300 mg/kg), one showed a decrease in A-a and A-b at Week 1 and one had a decrease in A-b at Week 2. All three dogs at 300 mg/kg died before the week 3 examination.
- Hematology and Clinical Chemistry - Elevated ALP (172 vs 8 IU/l) (1♂) and t-cholesterol (1♂, 493 vs 59.5 mg/dl; 1♀, 264 vs 159 mg/dl) were noted in some dogs at 300 mg/kg at Week 2.
- Necropsy -

  Organ Weights: Significantly increased organ absolute weights were noted in the lungs, liver, kidneys and adrenal glands of dogs at 300 mg/kg.

  Gross Pathology: No lesions were characterized in the dogs at 10 mg/kg/day. For the dogs at 50 mg/kg/day, reddish-brown spleen, and an ulcer in the jejunum were observed in 1♀ and hemorrhage in the urinary bladder was found in 1♂. Gastric ulcers and hemorrhage in the GI tract and urinary bladders were found in all dogs at 300 mg/kg. Lesions such as local necrosis in the liver (1/3), hemorrhage in the kidney (2/3), deep-blue nodules in the spleen (2/3) and red spots in the lungs (2/3) were also seen the dogs at 300 mg/kg.

  Histopathological Examination: Dilation of the blood vessels in the choroid near the optic papillae was seen in dogs at 10 (1 & 1♀) & 50 (1♀) mg/kg/day. Hemorrhage in the area between the iris and the ciliary body, in the anterior chamber and loosening of cornea epitheliums were noted in 1♂ at 300 mg/kg that had pinhole eye on Day 14. Thinning of cornea epithelium, dilations of the lymphatic vessels in the upper layer of the choroid, and dilation of the blood vessels in the choroid near the optic papillae were observed in 1♀ at 300 mg/kg.

3.6.1.2. Effect of the Continuous Administration of TBX on the Urinary Tract in Rats. (SR2316)(Vol. 1.13, p 56)

Report Nº:	SR2316
Study Nº:	88-802, MADI-H-21374
Compound:	Pemirolast Potassium (Lot Nº M-06) dissolved in distilled H_2O
Vehicle Control:	Distilled H_2O
Dose & Route:	50, 150 or 250 mg/kg/day po for 13 weeks in the study of Formation of Urinary Crystalline Matter (UCTM) and Bladder Stone; 250 mg/5ml/kg/day for 1 and 3 days and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 weeks in the study of Relationship between the Bladder Stone and the Epithelial Tissue of the Bladder Mucosa
Animal:	♂ SD rats, ~6 weeks of age, 10/group
Compliance with GLP/QAU:	Not Indicated
Study Site:	
Study Date:	Not Stated.

Results:

Formation of UCTM and Bladder Stones:

- General Condition, Body Weight, Food Consumption and Water Consumption - Periodic observations of lacrimation were noticed in animals at 250 mg/kg. One death occurred on Day 11. A dose-related suppression in weight gains was observed in treated animals **(No data were presented)**. A reduction in food consumption was seen in animals at 50 & 150 mg/kg. An increase in water intake was noted in rats at 250 mg/kg **(No data were presented)**.
- Urine Test - The specific gravity and urine pH were determined 1x/2-week. The results showed slightly elevated pH values and mildly decreased urine specificity in treated animals. These

changes were not dose-related. UCTM was observed in rats at ≥150 mg/kg from Day 1 of treatment. In contrast UCTM was not noted in the rats at 50 mg/kg/day until Week 7. Urine excretion was significantly increased in the rats at 250 mg/kg/day. A significant decrease in the excreted Na^+, K^+, and Cl^- was detected in the TBX-treated animals **(No data were presented)**. Urinary excretion of Ca^{2+} was increased in a dose-dependent manner **(No data were presented)**.

- Concentration of TBX and TBX-01 Metabolites in the Urine - TBX-01 was the major metabolite excreted in the urine; a small amount of parent compound TB was also present in the urine. The amount of excreted TBX-01 reached the maximum level of ~800 μg/ml as the dose increased during the treatment. The plateau was reached at Week 2 post administration in the rats at 250 mg/kg/day. **It appeared that there was ro correlation between the amount/pattern of excretion of TBX-01 and calculi formation.**
- Pathology - Calculi originated from TBX were found in the bladder of 8 (~89%) rats at 250 mg/kg/day. Histological examinations of bladders revealed simple hyperplasia (2/9), papillomatous hyperplasia, papilloma (1/9) and, edema and inflammation in the submucosal layers in the 250 mg/kg/day group. No abnormal changes in the bladder mucosa were observed in the groups receiving 50 and 150 mg/kg/day. Desquamation of epithelial tissue and cell **(the sponsor did not state what types of cells)** infiltration of mucosal membranes in the ureter were characterized in 1/9 at 250 mg/kg.

Relationship between the Bladder Stone and the Epithelial Tissue of the Bladder Mucosa:

- Relationship among UCTM, Bladder Stone and Epithelial Tissue of the Bladder Mucosa- The incidence (n=10) of UCTM, bladder stone and proliferative changes in the bladder epithelial mucosa are presented in the following table.

Changes	Day		Week												
	1	3	1	2	3	4	5	6	7	8	9	10	11	12	13
UCTM	0	8	10	10	10	7	8	9	8	9	9	10	9	10	9
Calculus	0	0	0	0	0	2	2	4	3	4	5	6	4	5	7
Histopathology*	0	0	0	0	0	0	0	2	3	1	5	6	3	5	8

* Histopathological changes of urinary bladder: simple hyperplasia, papillomatous hyperplasia or papilloma.

It appeared that the animals with bladder stones always had UCTM, and there was a positive correlation between the presence of bladder stones and the proliferative changes in the bladder epithelial mucosa.

- Pathology - The major lesions in the urinary bladder, ureter, and kidney were simple hyperplasia, papillomatous hyperplasia or papilloma in the urinary epithelial mucosal tissue, desquamation and acidophilic changes of bladder mucosa, dilation of renal tubules, and basophilic or acidophilic changes in the distal renal tubules. Ca-like material deposition in the kidney was also noted in some animals 9 weeks post dosing.

3.6.1.3. Maximization Test of TBX in Guinea Pigs. (SR2011)(Vol.1.27 p 101)

Report Nº: SR2011
Study Nº: SRT 401, 876314
Study Aims: To determine the potential of TBX to induce skin sensitization during ophthalmological application.
Compound: Pemirolast Potassium (Lot Nº M-10) dissolved in borate buffer, pH 8.0; 2% for intra-cutaneous route and 25% for skin application.
Positive Control: Dinitrofluorobenzene (DNFB)
Animal: ♂ Hartley guinea pigs, 5-week old, 12/group
Compliance with GLP/QAU: Yes (Japanese)

Study Site:

Study Date: 9/1987 - 12/1987

Study Designs & Results:

Group	Nº Animal	Induction Ag/Route	Day 21 Challenge for 24 hr	Maximizing Grading of Skin Reactions[c]			
				0	+1	+2	+3
1	12	None	150 mg 25% TBX ointment	9	3	0	0
			150 mg 1% DNFB ointment	12	0	0	0
2	12	Day 1: 2% TBX/IC[a]	150 mg 25% TBX ointment	12	0	0	0
		Day 7: 10% SDS[b] ointment					
		Day 8: 250 mg 25% TBX ointment for 48 hr					
3	12	Day 1: 0.1% DNFB/IC	150 mg 1% DNFB ointment	0	0	2	10
		Day 8: 250 mg 1% DNFB ointment					

[a] Intracutaneously.
[b] SDS = sodium lauryl sulfate.
[c] 0: none; +1: slight or scattered redness; +2: moderate red; +3: severe redness with edema or necrosis.

Based on the data shown in the above table, TBX appeared not to have skin-sensitizing properties.

3.6.1.4. Antigenicity Studies in Rabbits and Guinea Pigs. (SR2150)(Vol. 1.27, p 117)

Report Nº: SR2150
Study Nº: 86-1751
Study Aims: To evaluate the immunogenic potential of TBX in rabbits by subcutaneous injection with TBX, 1 mg/kg or TBX-rabbit sera, 1 ml/kg.
Compound: Pemirolast Potassium (Lot Nº M-06)
(+) Control: Egg albumin
Animal: ♀ New Zealand White Rabbits, 12-week.-old, weighing 2.25-2.78 kg; ♀ guinea pigs, 4-week-old, weighing 250-300 g
Compliance with GLP/QAU: Yes
Study Site:

Study Period: 3/11/1986 -2/23/1987
Study Designs: Immunization schedules were as follows:

Group	Animal Species	Nº of Animals	Immunogen	Dose of Immunogen (mg/kg)	Route of Immunization	Frequency
1	Rabbit	3	TBX + FCA	1	sc	1x/week x 4
2		3	TBX-RS + FCA	1	sc	1x/week x 4
3		3	OVA + FCA	1	sc	1x/week x 4
1	Guinea Pig	13	TBX	2	ip	1x/other day x 3
2		13	TBX	10	ip	1x/other day x 3
3		13	TBX-GS	2	ip	1x/other day x 3
4		8	OVA	2	ip	1x/other day x 3
5		13	TBX + FCA	2	sc	1x/week x 3
6		13	TBX-GS + FCA	2	sc	1x/week x 3
7		8	OVA + FCA	2	sc	1x/week x 3
8		13	TBX + Alum	0.01	ip	1x/month x 3
9		13	TBX + Alum	0.1	ip	1x/month x 3
10		13	TBX-GS + Alum	0.01	ip	1x/month x 3
11		13	OVA + Alum	0.0	ip.	1x/month x 3
12		8	TBX	20	po	5x/week x 10

FCA = Freund's Complete Adjuvant; RS = Rabbit Serum; GS = Guinea Serum

Results: The data from hemagglutination and PCA skin tests in rabbits plus PCA responses and systemic anaphylaxis reactions in guinea pigs showed that TBX was not immunogenic in both species.

4. LABELING REVIEW

DRAFT

LABELING

5. SUMMARY AND EVALUATION:

5.1. PHARMACOLOGY

5.1.1. MECHANISM -RELATED PHARMACOLOGY

TBX was demonstrated to:

- ↓ anaphylactic reaction in conjunctiva (allergic conjunctivitis) in rats, guinea pigs and rabbits;
- ↓ PGE_1 but not histamine, serotonin or bradykinin induced skin reaction in rats;
- ↓ homologous PCA in rats and guinea pigs;
- block antigen inhalation induced asthma;
- ↓ histamine release from (a) rat peritoneal mast cells and lung fragments, (b) human leukocytes and lung fragments and (c) guinea pig lung fragments induced by homologous IgE, compound 48/80 (a mast cell degranulator);
- ↓ antigen-induced conversion of phosphatidyllinosital 4,5-biphosphate and phosphatidylcholine to their second messengers, 1,2-diacylglcerol (1,2-DG), and phosphatidic acid (PA), respectively; and
- have no effects on Type II, II and IV hypersensitivity, and antibody titers to specific antigen such as SRBC and DNP-ovalbumin in rats or guinea pigs.

5.1.2. SAFETY PHARMACOLOGY

- TBX (0.1 & 1.0%) was shown to have no effect on pupil diameter and corneal sensory reaction;
- TBX, 250 mg/kg po for 30 days -
  - cytochrome P-450 content and NADPH-cytochrome C reductase activity: no effect;
  - cytochrome b_5 content: slight ↑;
  - NADPH-cytochrome b_5 reductase activity: significant ↓;
  - aminopyrine N-demethylase: slight ↑.
- TBX, at ≥1 mg/kg po, had antipyretic effect in Brewer's Yeast-induced hyperthermia rat model;
- TBX, at ≥10 mg/kg po - transient slight ↓ spontaneous motor activity in mouse;
- TBX, at ≥1 mg/kg iv - ↓ BP ↑ HR & ↑ blood flow in femoral artery; transit slight ↓ respiration in dogs;
- TBX, at $\geq 10^{-5}$ g/ml - ↑ rate and contraction dose-dependently in isolated guinea pig atria;
- TBX, at ≥0.1 mg/kg iv - slight ↓ in uterus spontaneous contraction in situ;
- TBX, at ≥100 mg/kg id - ↓ secretion of gastric juice, acid and pepsin;
- TBX, at 1, 10, 100 mg/kg po - no effects on liver function (BSP test), blood coagulation and GI tract; and
- TBX, at 100 mg/kg po - ↓ PSP excretion and ↑ urinary K^+ excretion.

5.1.3. RECEPTOR BINDING

Radioligand binding studies with rat brain membrane receptor systems demonstrated that TBX had little or no affinity for α_1-adrenergic, ß-adrenergic, muscarinic, cholinergic, histamine H_1, or dopamine D_2 receptors.

5.2. ADME

5.2.1. OCULAR

Following a single TBX (0.1%, 50 μl) instillation in rabbits, higher concentrations of TB (free acid of TBX) were found in extraocular tissues (palpebral conjunctiva, bulbar conjunctiva, cornea, and anterior sclera) than in intraocular tissues. Drug levels in the tissue and plasma declined over time. However, high levels of TB remained in the palpebral and bulbar conjunctival 24 hr post instillation. In contrast, plasma TB levels were not detectable by 4 hr post instillation of the drug.

Mean TB concentrations in conjunctiva (palpebral & bulbar) and aqueous humor after single and multiple (2x/day for up to 7 days) instillation in rabbits were also determined. TBX was not detectable in the aqueous humor 12 hr post either single or multiple (7 & 13x) instillation. TBX levels reached a steady state after 7 instillation by the evidence that similar concentrations were measured after 7 and 13 repeated instillation. After repeated instillation (7 & 13x), the concentrations of TB in conjunctiva and aqueous humor decreased over time implying that TB might not accumulate in the ocular tissues.

The plasma TBX and its metabolite TBX-01 levels on Days 14, 91, and 183 following ocular administration to rabbits for 6 months are shown in the following table. Generally, higher concentrations of TBX and TBX-01 were noted on Day 183 than Days 14 or 91 in 0.25% group, an indicative of accumulation.

Group	Day 14		Day 91		Day 183	
	♂	♀	♂	♀	♂	♀
TBX (ng/ml)						
0.1 % TBX	1.399 ± 0.750	1.318 ± 0.156	1.057 ± 0.482	0.733 ± 0.292	0.859 ± 0.397	1.545 ± 0.68
0.25% TBX	1.802 ± 0.508	2.592 ± 1.029	2.348 ± 0.702	2.262 ± 1.251	3.525 ± 2.354	4.732 ± 0.955
TBX-01 (ng/ml)						
0.1 % TBX	0.142 ± 0.156	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
0.25% TBX	0.042 ± 0.102	0.187 ± 0.153	0.116 ± 0.128	0.052 ± 0.127	0.743 ± 1.056	0.883 ± 1.279

The retainability of TBX (0.1%) in bulbar conjunctiva in rabbits after topical applications was studied in *in vivo* and *in vitro* settings. The results indicated that the retention of TB in conjunctiva appeared to be mucin-related. In addition, TBX did not bind to melanin, a carboxylated pigment with affinity for basic chloroquine diphosphate but not acidic drugs.

5.2.2. SYSTEMIC

5.2.2.1. Absorption (Bioavailability) and Toxicokinetics

- Rat, 50 mg/kg po for 4 weeks -

Summarized mean PK parameters for TBX following single and repeated oral dosing are presented in the following table. Higher plasma AUC and C_{max} values were obtained during Weeks 1 and 4 indicating that accumulation of TBX occurred following repeated oral dosing.

Parameters	Single Dose		Week 1		Week 4	
T_{max} (hr)	1	4	2	8	2	8
C_{max} (μg/ml)	1.8	4.4	19.4	16.4	22.9	40.4
AUC_{0-24} (μg•hr/ml)	76.8		246.9		499.6	

- Dog - The PK parameters in the plasma following single iv or oral administration to the dog are shown in the following table.

Parameters	Dose (mg/kg)- IV		Dose (mg/kg)- Oral		
	0.2	1	0.2	1.0	5.0
K_a (hr^{-1})	1.078 ± 0.071	1.044 ± 0.087	6.197 ± 1.131	3.965 ± 0.561	0.943 ± 0.181
K_e (hr^{-1})	-	-	0.984 ± 0.065	0.932 ± 0.098	0.667 ± 0.035
$T_{1/2}$ (hr)	0.668 ± 0.048	0.710 ± 0.071	0.732 ± 0.052	0.894 ± 0.193	1.064 ± 0.057

T_{max} (hr)	-	-	0.315 ± 0.043	0.555 ± 0.088	1.722 ± 0.313
C_{max} (μg/ml)	-	-	0.235 ± 0.015	0.996 ± 0.112	4.359 ± 0.564
V_d (L/kg)	6.191 ± 0.367	5.312 ± 0.284	-	-	-
CL (ml/min)	107.8 ± 9.4	91.3 ± 9.7	-	-	-
AUC (μg•hr/ml)	0.416 ± 0.026	2.567 ± 0.251	0.307 ± 0.027	1.737 ± 0.182	15.895 ± 1.563
Absolute BA (%)	-	-	75.5 ± 3.6	66.6 ± 4.6	-

- Food Effect - The food effect on plasma PK parameters for TBX was evaluated in dogs following a single oral dose of 0.2 mg/kg. Results showed that food reduced and delayed drug absorption from the GI resulting in lower C_{max} and AUC values.

5.2.2.2. Tissue Distribution

TBX was well distributed into the majority of tissues as demonstrated by a rat tissue distribution study. Following an oral dose of 1 mg/kg [^{14}C]TBX, the gastrointestinal tract tissues contained the highest concentrations of radioactivity, with high levels of radioactivity also found in liver, red blood cells, kidney, liver and lung. By 24 hours post dose, except in blood contents, the concentrations of radioactivity in most tissues were decreased.
Data from the whole-body autoradiography study showed that highly perfused tissues, namely liver, heart, lungs, and kidney and intestinal contents contained the largest amounts of radioactivity.

5.2.2.3. Metabolism

TBX was metabolized by a similar metabolic pathway in the dog and human. The metabolites identified in the urine and blood were TBX-01 (hydroxyl metabolite), TBX-02 (glucuronide of TBX), and TBX-03 (glucoside of TBX).
A study in rats showed that TBX at 250 mg/kg/day caused slight to moderate induction of hepatic drug metabolizing enzymes, aminopyrine N-demethylase and aniline hydroxylase, following repeated oral dosing.

5.2.2.4. Excretions

Studies in the rat and dog showed that urinary excretion was the major route for the elimination of TBX following a single oral or iv dose with values of 72-79% for the rat and ~67% for the dog, respectively. Urinary excretion stayed the same after multiple dosing with TBX. The remaining dose was eliminated through feces. TBX was metabolized extensively as little unchanged drug was excreted in urine. TBX-01, a hydroxyl metabolite, was the major metabolite excreted in rat urine. In contrast, the major metabolite excreted in the dog urine was TBX-03, a glucoside of TBX, which represented ~63% of dose eliminate within 48 hr post dosing.
In humans, the major metabolite excreted via urine was TBX-02, a glucuronide of TBX, which accounted for ~79% of the dose.

5.2.3. PLASMA PROTEIN BINDING

The ability of TBX to bind plasma protein was evaluated *in vitro* using the micropartition centrifugation method. The binding of TBX to the serum protein varied from species to species. TBX at concentrations of 0.1-2.5 μg/ml showed protein binding to human serum, human serum albumin, rat serum and dog serum of approximately 96%, 96%, 84%, and 66%, respectively.

5.2.4. PLACENTAL TRANSFER AND MILK SECRETION

Secretion of TBX through milk was evaluated in the lactating SD rats by given a single oral dose of 1 mg [^{14}C]TBX via gavage. The concentrations of TBX in and milk were either similar to or higher

than maternal plasma, indicating that TBX was distributed to milk and readily available to the neonate.

Placental transfer of TBX was studied by giving a single oral dose 1 mg/kg [^{14}C]TBX to pregnant rats at GD 18. Results showed that low but detectable levels of TBX in fetal blood and tissues, indicating that TBX crossed the placenta and was available to the fetus.

5.3. TOXICOLOGY

5.3.1. OCULAR TOXICITY

The potential of TBX to induce ocular toxicity was evaluated in rabbit following single day/frequent instillation (1 drop/instillation, 10x/day), and multiple applications (4x/day) for either 28-day, 91-day and 6-month. It appeared that TBX, up to 0.25%, did not cause any eye irritation and injury following 6-month ocular application. The results from each study were summarized in the following table.

Species N°/group	Dose TBX (%)	Dosing Frequency	Dosing Duration	Findings
Japanese Albino Rabbit 5♂/group	0.1, 0.5, 1%, vehicle, or saline	1 drop, 10x/day	1 day	Signs of nictitating membrane congestion were noted in one each rabbit @. 0.1, 0.5% TBX.
Japanese Albino Rabbit 7♂/group	0.1%, vehicle, or aged 0.1%[a]	1 drop, 10x/day	1 day	↔[c]
Japanese Albino Rabbit 6♂/group	0.1%, light-exposed 0.1%[b], vehicle	1 drop, 10x/day	1 day	↔
Japanese Albino Rabbit 10♂/group	0.1, 0.5, 1%, vehicle	1 drop, 4x/day	28-day	↔
Japanese Albino Rabbit 10♂/group	0.1%, vehicle	1 drop, 4x/day	91-day	Lesions of right testicular and epididymal atrophy were identified in 1/10 TBX-treated rabbits.
Hra:NZW (SPF) Rabbit 6/sex/group	0, 0.1, 0.25%	1 drop, 4x/day	6-month	↔

[a] The 0.1% pemirolast potassium solution was previously stored at 40°C at 75% relative humidity for six months.

[b] The 0.1% pemirolast potassium solution was previously exposed to 600,000 lux•hours of light.

[c] ↔ = No effects.

5.3.2. SYSTEMIC TOXICITY

5.3.2.1. Acute (Single-Dose) Toxicity

Acute single-dose toxicity of TBX was evaluated in three different species, mice, rats and dogs. Summarized findings are presented in the following table.

Species Strain	Route	Dose (mg/kg)	LD_{50} (mg/kg)	Findings
Mouse Crj:CD-1 (ICR) 10/sex/group	po	1030-2740	1250	**Clinical Signs:** ↓ locomotor activity, somnolence, and convulsions; most deaths occurred within 3 hr post dosing. **Pathology:** hemorrhaging in the gastric intestinal organs (po); hemorrhaging in subcutaneous area (sc); and hemorrhaging in the lungs (iv).
	sc	410-800	550	
	iv	139-415	250	
Rat Crj:CD (SD) 10/sex/group	po	500- 1790	725	**Clinical Signs:** ↓ locomotor activity, somnolence, salivation, lacrimation, perspiration, dyspnea, tachypnea, salivation, lacrimation, erect tail, and convulsions; most deaths occurred within 3 hr post dosing. **Pathology:** hemorrhages in the stomach and intestines(po); subcutaneous bleeding, hemorrhages in the lung, glandular stomach and intestines, spotty bleeding in the thymus (sc); and hemorrhages in the lungs and spotty bleeding (iv).
	sc	310-620	450	
	iv	260-530	380	
Dog Beagle 2♂/group	po	60, 600, 6000	>6000	**Clinical Signs:** Emesis, salivation, tarry stool, ↓ appetite and slight reddening of oral mucosa and conjunctiva. **Pathology:** slight red-tinted jejunum mucosa (1 @ 60 mg/kg), slight red-tinted in duodena and ileum (1 @ 600 mg/kg), and hemorrhages in ileum mucosa (1 @ 6000 mg/kg). **Histopathology:** thickening of the alveolar septum (1 @ 60 mg/kg), lymphocyte infiltration around bronchi and round cell infiltration in the interstitium in the kidney (1 @ 6000 mg/kg), and leukocyte infiltration in the pancreases and round cell infiltration in the interstitium in the kidney (1 @ 6000 mg/kg).

5.3.2.2. Repeated-Dose Toxicity

The repeated-dose toxicity of TBX was conducted in three species, mice, rats and dogs. A summary of results obtained from each study is listed in the following table.

Species	Dose Levels (mg/kg)	Duration	Findings	NOAEL
$B6C3F_1$ Mouse 10/sex	0, 1250, 2500, 5000, 10000 ppm in diet (♂: 0, 147, 306, 585, unknown mg/kg/day; ♀: 0, 188, 398, 664, unknown mg/kg/day)	13-wk	10000 ppm: All mice died or sacrificed within 7 days with signs of emaciation, hypothermia and crouching prior to death. 5000 ppm: A dose dependant ↓ in mean body weight with range values of 4-22%; ↓ food consumption; Slight ↑ in LDH (1.3-1.5x) and ALP (♂ only, 1.2x); ↑in a typical or immature epithelial cells and crystalline urine. Rhomboid shape crystals were also seen in the urine of animals @ 2500 ppm. Gross Pathology - Gonadal atrophy (♂+♀) and calculi in bladder (♂) were noted in mice @ 5000 ppm. Histopathology - Cytoplasmic vacuolation of mucosal epithelium urinary bladder, frequently associated with eosinophilic cytoplasmic droplets, hemorrhage, epithelial hyperplasia, inflammation, and calculus deposition in 5/10 ♂ and 10/10 ♀ at 5000 ppm; cytoplasmic vacuolation and necrosis in liver at 10,000 ppm.	2500 ppm
Fisher Rat 10/sex	0, 1250, 2500, 5000, 10000 ppm in diet. (♂: 0, 74, 149, 306, 592, mg/kg/day; ♀: 0, 73, 153, 303, 607 mg/kg/day)	13-wk	10000 ppm: markedly ↓feed consumption (♂: 62%→27%; ♀: 51→6%), ↑ H_2O (♂: ↑1.4-2.2x; ♀: ↑1.3-1.6x); ↓ in RBC (↓11-18%), hematocrit (12-15%) and Hb (11-13%) with ↑ reticulocyte counts (29-53%); ↓ in WBC (↓26%) and absolute segment PMN counts (↓34%) in ♂; ↓ urine pH (5.5-7.5 vs 7.5-8.0); ↑ the frequency of occult blood (+); ↑ urine excretion by 3.5x for ♂ and 1.6x for ♀; ↑ RBC in the urine. Transient ↓ in food intake (↓18→7%) was noted in ♂ @ 5000 ppm. Organ weight: ↓ relative and absolute weights of testes (↓65 and 30%, respectively) and ovaries (↓41 and 21%, respectively) and ↑ relative and absolute kidney weights (↑12%, ♀ only) in 10000 ppm; ↑ relative liver weights (8-20%) in ♂ at ≥1250 ppm. Gross Pathology - only identified in 10000 ppm group: calculi in the kidney, ureter, and/or urinary bladder; enlarged kidney and ureterectasis (5♂); slight to severe thymic atrophy (9♂ & 5♀), slight or slight →moderate atrophy of testes (9/10), epididymis (9/10), seminal vesicle (9/10) and prostate gland (9/10), slight→moderate atrophy of uterus (6/10) and ovaries (slight, 4/10), and slight →severe dilation of urinary tract (5♂ & 7♀). Histopathology: *Kidney* - slight→severe dilation of the renal tubules (10♂ & 9♀), hyperplasia of the pelvic epithelium (9♂ & 9♀, slight→severe), and inflammation (7♂ - slight→severe & 2♀ - slight) and fibrosis (3♂ - moderate→severe, & 1♀ - slight) in rats at 10000 ppm; *Urinary Bladder* - moderate→severe hyperplasia of mucosal epithelium (6♂ @ 2500 ppm; 10♂ & 3♀ @ 5000 ppm; 7♂ & 6♀ @ 10000 ppm) and inflammation with characteristics of hemorrhaging and edema with infiltration of neutrophils and lymphocytes (4♂ @ 2500 ppm; 10♂ @ 5000 ppm; 7♂ & 4♀ @ 10000 ppm) were identified; *Others* - Granuloma in the parenchyma of the liver was detected in 1♀ at 5000 ppm and calcification in the muscle layer of the stomach was noted in one control female.	♂: 1250 ppm ♀: 2500 ppm
Rat Crj:CD(SD) 15-22/sex/group	0, 5, 10, 50, 250 qd po	13-wk + 5-wk recovery	250 mg/kg: Two rats died with clinical observations of transient salivation and loose feces; ♂ rats had marked ↓ in cumulative (↓18%) weight gain accompanied with lower mean body weight (↓5-11%) during the treatment and the 1st three weeks of recovery phase and ↓ food intake (↓8-9%) at Weeks 1-2, ↑ H_2O uptake (↑13-68%) from Weeks 2 to 17 (4 wk after drug withdraw); a ↓ in urine specific gravity (1.045 vs 1.051 in controls), an ↑ in the urine volume (15.4 vs 6.5 ml/rat/16 hr) & turbidity, a (+) occult blood (4/15) and an ↑ in the frequency of the appearance of epithelial cells (12/15 vs 7/15 in controls) for the ♂; ↑ urine volume (12.5 vs 8.4 ml/rat/16 hr) & turbidity for the ♀; ↑ in total bilirubin (1.9x), GTP activity (1.3x), and creatinine (1.4x) and ↓ in glutathione (↓26%) and NEFA (↓35%) in ♂; ↑ total bilirubin (1.6x) & ↓ glutathione (↓25%) in ♀. Organ Weight and Gross Pathology - slightly ↑absolute (♂, ↑4-7%; ♀, ↑13%) and/or relative liver weight (♂, ↑7-18%; ♀, ↑20%); ↑ spleen weight (♂, ↑17%), ↓ thymus weight (♂: ↓33%), and ↓ testicular weight (5-6%); ↑ the relative (♀, 10%)/absolute (♀, 18%) weight of submaxillary; gastric ulcer (9/14♂ & 2/15♀), enlarged kidney (2/14♂), and yellowish-white crystalline calculi in the bladder (4/14♂; 1/5♂ of recovery phase). Histopathology: *Kidney* - anemic glomeruli; dilatation of proximal renal tubules, distal renal tubules or collecting tubule; transitional epithelium hyperplasia (7♂ & 1♀); *Urinary Bladder* - transitional epithelium papillary hyperplasia with cellular infiltration (9♂); *Stomach* - mucosal epithelium ulceration (11♂ & 2♀)	50 mg/kg/day

Species	Dose Levels (mg/kg)	Duration	Findings	NOAEL
Beagle Dog, 4-6/sex/group	0, 10, 50, 150 qd po	13-wk + 5-wk recovery	150 mg/kg: 2 deaths with clinical observations of lowered body temperature, nasal hemorrhages, tarry stools, dislocation of the crystalline lens, and tremors prior to death; vomiting, reddening of the conjunctiva, palpebral sebum, decreased spontaneous movements, corneal turbidity, wasting, and dehydration were major signs during the treatment; a ↓ in food (♂: ↓16-52% during Weeks 2→5; ♀: ↓7-53% during Weeks 1→6) and H_2O intake (♂: ↓50-61% during Weeks 2→4; ♀: ↓42-61% during Weeks 2→5) accompanied by body weight loss seen in the dogs that died or sacrificed during treatment; reversible ↓ in the amplitude of a-waves, b-waves and o-waves; ↓ RBC (♂: ↓23 and 17%; ♀: ↓23 and 17%, respectively), Ht (♂: ↓20 and 7%; ♀: ↓24 and 12%, respectively) and Hb (♂: ↓23 and 7%; ♀: ↓23 and 12%, respectively) for the ♂ and ♀ at Weeks 5 & 13; ↑ LDH in ♂ & ♀ (312-330 IU/l vs 129-161 IU/l in controls) at Week 5. Organ Weight - ↓ in the absolute and relative weights of the testes during terminal sacrifice (↓~71%) and recovery sacrifice (↓~24%) in ♂ Gross Pathology - dislocation of the crystalline lens with lesions of necrosis and hemorrhage, ulceration of gastric mucosa, thymic atrophy, dark reddening of mesenteric lymph nodes, enlarged thyroid, and pale mucosa. histopathology - pulmonary edema, mild localized pneumonia foci, slight atrophy of the spleen, hyperplasia of the red pulp, moderate atrophy of the prostate epididymis, and testes with decreased sperm, erosion or ulcers or congestion in the GI tract, and atrophy of bone marrow and mesenteric lymph nodes in the dogs at 150 mg/kg that died or were sacrificed during the dosing period; ↓ sperm and atrophy of the reproductive organs in the ♂ during the terminal sacrifice.	50 mg/kg
Rat Crj:CD (SD) 10/sex/group	0, 2, 10, 50, 150 po	52-wk	150 mg/kg, ♂ only- ↓ mean body weight (↓9-17% at Weeks 16→52), decreased cumulative (Weeks 0-52) weight gain by 21%, ↑ water intake (15-65% at Weeks 6 →49) and a transient ↑ (12%) in food intake at Week 33; ↑ urine volume at Week 26, ↓ urine specific gravity at Weeks 26 & 51, ↑ the presence of RBC and round cells in the urine sediment at Week 51, and crystalline urine in 3/10, 1/10, 5/10, 9/10 at Weeks 14, 26, 40, and 51, respectively. Gross Pathology - calculi in the urinary bladder (17/20). Histopathology - *urinary bladder*: papillomatosis (13), transitional cell hyperplasia (2) and carcinoma (2) and hemorrhages (4), mild cellular infiltration (1); *kidney*: dilation of the distal renal tubules (7)	♀: 150 mg/kg ♂: 50 mg/kg
Beagle dog, 4/sex/group	0, 2, 10, 50, 75 in capsules po	52-wk	No deaths, vomiting was the major clinical observation. histopathological examine showed hepatic congestion (2/4♂), hepatocellular vacuolization (1/4♂) and cystic pituitary lesions (2/4♂).	75 mg/kg/day

5.4. CARCINOGENICITY

Two studies (mouse and rat studies) were conducted to evaluate the carcinogenic potential of TBX.

- Mouse Study [0, 70, 200, 625 ppm (≈ 0, 7, 20, 67 mg/kg/day) via diet admix for 78-week] - There were no significant changes in survival rate, hematology, urinalysis, gross pathology and histopathology. The length of study was not adequate and not every tissue collected from each group was subjected to microscopic examination. Therefore, no conclusions could be drawn from this study.
- Rat Study [0, 70, 200, 625 ppm (≈ 0, 3, 8.5, 88 mg/kg/day) via diet admix for 104-week] - No apparent effects on the survivals, body weight, food consumption, and clinical pathological parameters were observed. No drug-related alterations in histopathology were identified. Tumors were identified in 100, 100, 96, and 100% of the ♂ and 68, 54, 58, and 60% of the ♀ in the 0, 70, 200 and 625 ppm groups, respectively. Much higher Nº of ♂ at 625 ppm had more multiple tumors than the controls (82 vs 65%). Endometrial stromal polyps were found more often in the TBX treated rats with frequency of 8, 6, 16, and 22% in the control, 70, 200 and 625 ppm, respectively. The MTD was not reached. In addition, some tissues form 70 and 200 ppm groups were not examined; therefore, statistical analysis for the trend incidence in some tumor findings can not be performed.

5.5. REPRODUCTIVE TOXICOLOGY

The following table summarizes the effects of TBX on fertility, reproductive functions, embryo-fetal development, and peri-/post-natal development.

Species	Dose/Route (mg/kg)	Dosing Duration	Findings
Fertility, Early Embryonic Development → Implantation (Segment I)			
Rat Crj:CD(SD) 6-wk old 24/sex/group	0, 10, 50, 250, 400 po	♂: 7-wk prior to mating→ copulation; ♀: 2-wk prior to mating→ GD 7	≥250 mg/kg: deaths (2/24♂ and 6/24♀ @ 400 mg/kg; 2/24♂ @ 250 mg/kg), salivation, ↓ body weight and food intake at 250 and 400 mg/kg; ↑ preimplantation loss, ↓ implants, ↑dead or resorbed fetuses, ↓ number live fetuses at 400 mg/kg. **Gross Pathology**: A ↓ in the absolute epididymis weight; calculi in the urinary bladder, enlargement and pale kidneys were major gross findings for the ♂ at ≥250 mg/kg. NOAEL for parental, reproductive and developmental toxicities were 50, 50 and 400 mg/kg/day, respectively
Teratology - Embryo-Fetal Development (Segment II/III)			
Rat Crj:CD(SD) 12-wk old 36♀/group	0, 10, 50, 250, 400 po	Gestation Day 7→17	≥250 mg/kg: salivation, ↓ body weight gain and food intake; ↑ mean gestation period; no significant effect on number corpora lutea, implantations, resorptions, live fetuses; fetal growth retardation and ↓ fetal weight; ↓ live offspring at Day 4 postpartum (400 mg/kg group only, 80.3% vs 99.3%); no differences in neonatal development, behavior, or reproductive performance for surviving F_1 pups. The effects on the live fetuses included: ↑ thymic remnant in the neck, ↑ interventricular septal defect and dilation renal pelvis/ureter (400 mg/kg only), ↑ Nº of fetuses with variations, ↑ Nº of fetuses with wavy rib, ↓ Nº of ossified sternebrae (5th & 6th), sacral and caudal vertebrae, and metatarsus; and ↑ splitting of thoracic vertebral body (400 mg/kg only). NOAEL for parental, reproductive, developmental and neonatal (perinatal and postnatal) toxicities were 50, 50, 50 and 50 mg/kg/day, respectively.
Rabbit NZW 5-mon old 18♀/group	0, 5, 20, 50, 150 po	Gestation Day 6→18	150 mg/kg: ↓ weight gain and 7 does aborted; slight but not statistical significant ↑ in total Nº of fetal deaths and ratio of Nº of fetal deaths/Nº of implants. No changes in maternal organs or fetal abnormalities were seen. NOAEL for parental, reproductive, and developmental toxicities were 50, 150, and 150 mg/kg/day, respectively.
Perinatal/Postnatal Development (Segment III)			
Rat Crj:CD(SD) 12-wk old 24♀/group	0, 10, 50, 250, 400 po	Gestation Day 17 → Postpartum Day 21	≥250 mg/kg: deaths (7/24♀ @ 400 and 3/24♀ at 250 mg/kg), salivation, ↓ mean body weight gain and food consumption in all treated animals during GD 17-21; ↓ live births, ↓ implantations, ↓ birth rate and ↑ Nº of stillbirths for the dams @ 400 mg/kg/day; atrophy of the thymus and spleen, softening of the kidneys, scattered spots on the glandular stomach in dams having incompetence in nursing (250 & 400 mg/kg/day); and microscopic changes characterized as hydropic vesicles in the kidney, thymic atrophy, distended and thickening small intestine, and white patches on the kidney. **Effect on F_1**: ↓ 4-day survival ; ↓ mean body weight in F_1 from birth through day 70; a delay in incisor eruption, vaginal opening, eyelid separation and descent of testis, and ↓ absolute organ weights of kidney, spleen, adrenal, testes, ovaries, lungs, and heart; ↓ in the Nº of corpora lutea, Nº of implantation, Nº of live fetuses; atrophy of testis and epididymis (3 @ 250 mg/kg). Reduced absolute testis and epididymis weights. NOAEL for parental, reproductive and neonatal (perinatal and postnatal) toxicities were 50, 50 and 50 mg/kg/day, respectively

5.6. GENOTOXICITY

The genotoxic potentials of TBX were evaluated in both *in vitro* and *in vivo* systems and results from each study are presented in the following table.

Test Type	Indicator System	Compound	Dose	Results
Ames Bacterial Reverse Mutation	*Salmonella typhimurium*: TA 100, TA 1535, TA 98, TA 1537, TA 1538 *Escherichia coli*: WP2 uvr A	TBX	+/-S9: 10-5,000 μg/plate	Not mutagenic.
Ames Bacterial Reverse Mutation	*Salmonella typhimurium*: TA 100, TA 1535, TA 98, TA 1537, TA 1538 *Escherichia coli*: WP2 uvr A	TBX-01	+/-S9: 10-5,000 μg/plate	Not mutagenic.
Ames Bacterial Reverse Mutation	*Salmonella typhimurium*: TA 100, TA 1535, TA 98, TA 1537, TA 1538	TBX	+/-S9: 100-5,000 μg/plate	**Results were inconclusive as either the positive control was not working or no appropriate positive controls were included.**
Chromosome Aberration	Chinese Hamster Lung Fibroblasts	TBX	-S9: 94-750 μg/ml +S9: 375-3,000 μg/ml	Not clastogenic.
CHO/HPRT Forward Gene Mutation	Chinese Hamster ovary (CHO) cells	TBX	-/+S9: 250-1000 μg/ml	Not mutagenic.
Unscheduled DNA Synthesis (UDS)	*Primary Rat Hepatocytes*	TBX	100-1000 μg/ml	Did not increase unscheduled DNA synthesis.
In Vivo Cytogenetic Assay	Rat	TBX	62.5-250 mg/kg ip SD*	Not clastogenic.
Micronucleus	Rat	TBX	0, 50-400 mg/kg po SD	Not clastogenic.
			0, 25-200 mg/kg po x 5	

* SD = Single Dose

5.7. SPECIAL TOXICITY

5.7.1. EFFECTS ON VISUAL ORGANS

TBX was assessed for its potential effects on visual organs in the dog following a single iv or 21-day repeated oral administration. The results are summarized as followings:

- Single IV Administration (0.5, 10, and 200 mg/kg) - Salivation, abnormal gait, pinhole pupils and deaths were observed in dogs @ 200 mg/kg. Dose-dependent but reversible abnormal ERG (a slight to marked decrease in A-a and A-b waves) with normal ophthalmofundoscopic readings was noted in all dose groups at 15-180 min post doing, indicating that TBX might cause abnormal photoreceptor cells and defective retinal neuron functions temporarily. Ulcers and red spots in the stomach, red spots in the gall bladder, red spots in the entire GI tract were observed in one dog at 200 mg/kg that died one day post dosing. Histopathological examination showed congestion and hemorrhage in the iris, and a slight cellular infiltration in the iris and ciliary body were found in one dog at 200 mg/kg that died during test; a slight cellular infiltration in the space between the iris and the cornea (1/3) and a partial loosening of corneal epithelium (2/3) were identified in dogs @ 0.5 mg/kg. No abnormalities were noted in dogs @ 10 mg/kg.
- 21-Day Oral Administration (10, 50, and 300 mg/kg) - Vomiting, soft/bloody stools, body weight loss and deaths (3/3) were noted in dogs at 300 mg/kg. One dog @ 300 mg/kg had severe pinhole pupils, hemorrhage in the eye chambers of both eyes, and reddening of the conjunctiva of both eyes. In the high dose group (300 mg/kg), one showed a decrease in A-a and A-b at Week 1 and one had a decrease in A-b at Week 2. Elevated ALP and t-cholesterol were noted in some dogs at 300 mg/kg at Week 2. Significantly increased absolute organ weights of the lungs, liver, kidneys, and adrenal glands were noted in dogs at 300 mg/kg. For the dogs at 50 mg/kg/day, reddish-brown spleen and an ulcer in the jejunum were observed in 1♀ and hemorrhage in the urinary bladder was found in 1♂. Gastric ulcers and hemorrhage in the GI tract and urinary bladders were found in all dogs at 300 mg/kg. Lesions such as local necrosis in the liver (1/3), hemorrhage in the kidney (2/3), deep-blue nodules in the spleen (2/3) and red spots in the lungs (2/3) were also seen the dogs at 300 mg/kg. Histopathological examination showed hemorrhage in the area between the iris and the ciliary body, in the anterior chamber and loosening of cornea epitheliums in the ♂ at 300

mg/kg that had pinhole eye. Thinning of cornea epithelium, dilations of the lymphatic vessels in the upper layer of the choroid, and dilation of the blood vessels in the choroid near the optic papillae were observed in 1♀ at 300 mg/kg.

5.7.2. EFFECTS ON URINARY TRACT

The potential effects on urinary tract were evaluated in rats following repeated oral dosing with 0, 50, 150 or 250 mg/kg/day of TBX for 13 weeks. Results revealed that TBX caused formation of urinary crystalline matter (UCTM) after one day of treatment at doses ≥150 mg/kg/day. In contrast, UCTM was not detected until 7 weeks post treatment when rats treated with TBX at 50 mg/kg/day. Calculi were found in ~89% of rats @ 250 mg/kg. The major pathological lesions identified in the urinary bladder, ureter, and kidney of rats @ 250 mg/kg included simple hyperplasia, papillomatous hyperplasia or papilloma in the urinary epithelial mucosal tissue, desquamation and acidophilic changes of bladder mucosa, dilation of renal tubules, and basophilic or acidophilic changes in the distal renal tubules. Ca-like material deposition in the kidney was also noted in some animals in 250 mg/kg group at Week 9 post dosing.

5.7.3. ANTIGENICITY AND SKIN-SENSITIZING PROPERTIES

TBX did not appear to have skin-sensitizing properties in the guinea pig maximization test. In addition, TBX was not immunogenic by the evidence that it could not induce antibody formation and PCA skin reaction in the rabbits and systemic anaphylaxis reaction in guinea pigs.

6. CONCLUSIONS and RECOMMENDATION:

Pemirolast Potassium (TBX), a newly developed pyrido-pyrimidine agent, was demonstrated to have anti-allergic (a mast cell stabilizer) properties by the inhibition of antigen-induced allergic conjunctivitis in guinea pigs, rats, and rabbits. It has been marketed in Japan for the treatment of various allergic indications in systemic (bronchial asthma: 10 mg po bid; allergic rhinitis: 5 mg po bid) or ophthalmic (vernal and allergic conjunctivitis: 0.1% ophthalmic solution, 1 drop bid) applications. In addition, 0.1% pemirolast potassium is registered in China and Korea for the treatment of allergic and vernal conjunctivitis.

Preclinical acute ocular toxicology studies showed that TBX (0.1, 0.5 or 1.0%) following single day/frequent applications (1 drop/instillation, 10x/day), and multiple applications (4x/day) for either 28 days, 91 days or 6 months did not cause any eye irritation or damage in rabbits. Additionally, neither aged (stored at 40 °C, 75% relative humidity for 6 mon) nor light-exposed (600000 lux•Hr) TBX (0.1%) did cause ocular irritation in the rabbit following single day/frequent applications (1 drop/instillation, 10x/day). However, results from the preclinical systemic (acute, subacute and chronic) toxicity studies in rats (≥250 mg/kg for 13 weeks), mice (≥5000 ppm for 13 weeks) and dogs (200 iv single dose or ≥50 mg/kg po for 21 days) showed that TBX did cause systemic toxicity after oral and/or intravenous administrations.

Results of mouse carcinogenicity study were inconclusive as the length and designs of the study are not acceptable by the current regulatory standards. As for the rat carcinogenicity study, due to lack of observed adverse effects at all doses, the MTD was not achieved. Additionally, statistical analysis for the trend incidence for various tumors can not be performed as most of tissues from low- and mid-dose groups were not examined in both mouse and rat studies. Therefore, information derived from both studies was ambiguous and should not be included in the labeling.

Approval of 0.1% pemirolast potassium ophthalmic solution is recommended.

7. INFORMATION TO SPONSOR:

1) Some study reports are in such poor quality and require extra time to complete review process. The sponsor is encouraged to improve the quality and organization of future submissions.

2) When foreign study reports are included in the submission, the sponsor is encouraged to ensure the accuracy and comprehensibility of English translation.

3) The labeling should reflect any reported significant observations.

/S/ 7/30/99
W.C. Josie Yang, DVM, Ph.D.

Concur by team leader: Yes ☒ No ☐

/S/ 7.30.99
Andrea Weir, Ph.D.

cc:
NDA 21-079
HFD-550/Division File
/JYang
/WBoyd
/AWeir
/RRodriguez
HFD-345
F/T by JYang, July 30, 1999

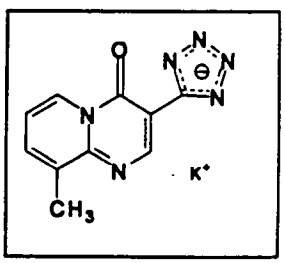
APPEARS THIS WAY
ON ORIGINAL

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS

PHARMACOLOGY AND TOXICOLOGY REVIEW Nº 2

NDA	**21-079**
DRUG:	Alamast [Pemirolast Potassium Ophthalmic Solution, 0.1%]
CODE NAMES:	TBX, BMY-26517, DE-068
SPONSOR:	Santen Incorporated 555 Gateway Drive Napa, CA 94558
SUBMISSION DATE:	March 25, 1999
TYPE OF SUBMISSION:	Original, 505 (b) (1)
DATE COMPLETED:	August 10, 1999
REVIEWER:	W. C. Josie Yang, DVM, Ph.D.
INFORMATION TO SPONSOR:	No
CDER STAMP DATE:	March 26, 1999
DATE RECEIVED IN HFD-550:	March 29, 1999
DATE ASSIGNED TO REVIEWER:	April 1, 1999
USER FEE DUE DATE:	September 26, 1999
DRUG CATEGORY:	Anti-allergic Agent (Mast Cell Stabilizer)
FORMULA:	$C_{10}H_7N_6KO$; 1-methyl-3-(1H-tetrazol-5yl)-4H-pyrido[1,2-a] pyrimidin-4-one-potassium; MW=266.3

Ingredient	Quantity(mg/ml)	Percent (w/v)
Pemirolast potassium		
Lauralkonium chloride		
Glycerin		
Dibasic sodium phosphate,		
Monobasic sodium phosphate		
Sodium hydroxide		
Phosphoric Acid		
Purified water		



CAS Nº:	100299-08-9
INDICATION:	Allergic Conjunctivitis
DOSAGE FORM:	0.1% ophthalmic solution
RELATED DRUG/INDs/NDAs/DMFs:	INDs [redacted] DMFs [redacted]

Revised Labeling Review:

The following revised statement reflects the results obtained from *in vitro* and *in vivo* genotoxicity assays and should be included in the labeling:

[redacted]

APPEARS THIS WAY
ON ORIGINAL

/S/ 8/10/99
W.C. Josie Yang, DVM, Ph.D.

Concur by team leader: Yes ☒ No ☐

/S/
Andrea Weir, Ph.D. 8-10-99

cc:
NDA 21-079
HFD-550/Division File
/JYang
/ AWeir
/ WBoyd
/RRodriguez

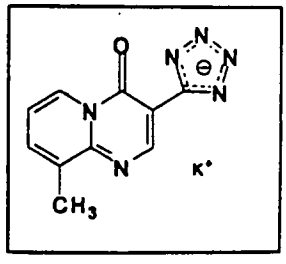
APPEARS THIS WAY
ON ORIGINAL

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS

PHARMACOLOGY AND TOXICOLOGY REVIEW Nº 3

NDA	**21-079**
DRUG:	Alamast [Pemirolast Potassium Ophthalmic Solution, 0.1%]
CODE NAMES:	TBX, BMY-26517, DE-068
SPONSOR:	Santen Incorporated 555 Gateway Drive Napa, CA 94558
SUBMISSION DATE:	March 25, 1999
TYPE OF SUBMISSION:	Original, 505 (b) (1)
DATE COMPLETED:	September 23, 1999
REVIEWER:	W. C. Josie Yang, DVM, Ph.D.
INFORMATION TO SPONSOR:	**No**
CDER STAMP DATE:	March 26, 1999
DATE RECEIVED IN HFD-550:	March 29, 1999
DATE ASSIGNED TO REVIEWER:	April 1, 1999
USER FEE DUE DATE:	September 26, 1999
DRUG CATEGORY:	Anti-allergic Agent (Mast Cell Stabilizer)
FORMULA:	$C_{10}H_7N_6KO$; 1-methyl-3-(1H-tetrazol-5yl)-4H-pyrido[1,2-a] pyrimidin-4-one-potassium; MW=266.3

Ingredient	Quantity(mg/ml)	Percent (w/v)
Pemirolast potassium		
Lauralkonium chloride		
Glycerin		
Dibasic sodium phosphate		
Monobasic sodium phosphate		
Sodium hydroxide		
Phosphoric Acid		
Purified water		



CAS Nº:	100299-08-9
INDICATION:	Allergic Conjunctivitis
DOSAGE FORM:	0.1% ophthalmic solution
RELATED DRUG/INDs/NDAs/DMFs:	INDs DMFs

1.1. **REVISED LABELING:**

The following revised statement reflects the recommendations by Dr. Abby Jacobs, Associate Director of Pharmacology/Toxicology for ODE5:

1.2. **CALCULATION OF HUMAN DOSE MULTIPLES**

According to center policy, the dosages used in animals need to be converted to human equivalent doses based on comparative serum/plasma levels, AUC and if data of drug exposures in animal studies are not available, the determination of human exposure multiples should be based on the conversion of body surface exposure. However, a request was made by the medical review team leader, Dr. Wiley Chambers, to derive human exposure multiples based on mg/kg instead of the conversion of body surface exposure mg/m^2 to appear in the current labeling.

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/23/99
W.C. Josie Yang, DVM, Ph.D.

Concur by team leader: Yes ☒ No ☐

/S/ 9-24-99
Andrea Weir, Ph.D.

cc:
NDA 21-079
HFD-550/Division File
/JYang
/ AWeir
/ WBoyd
/Rrodriguez
F/T by JYang, September 23, 1999

APPEARS THIS WAY
ON ORIGINAL

HFD-550
R. RODRIGUEZ

REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

JUN 27 1999

June 18, 1999

A. 1. NDA 21-079

SPONSOR Santen Incorporated
555 Gateway Drive
Napa, California 94558

2. PRODUCT NAMES: Pemirolast Potassium Ophthalmic Solution, 0.1% (Alamast™)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Ophthalmic solution - of 10 mL [redacted] 10 mL [redacted]

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Inhibitor of Type I immediate *in vivo* hypersensitivity

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: March 25, 1999

2. DATE OF AMENDMENT: none

3. RELATED DOCUMENTS: DMF [redacted] DMF [redacted] and IND [redacted]

4. ASSIGNED FOR REVIEW: April 7, 1999

C. REMARKS: The drug product is manufactured [redacted]

[redacted]

D. CONCLUSIONS: The submission is approvable pending resolution of the comments and deficiencies noted. [redacted]

/S/ 6-18-99

David Hussong, Ph.D.

APPEARS THIS WAY ON ORIGINAL

/S/ 6/22/99

cc:

HFD 160/Consult File
HFD 550/R. Rodriguez/CSO
HFD 550/Chemist/R. Uppoor /S/
HFD 805/D. Hussong
HFD 550/ Boyd

Drafted by: D. Hussong, 06/18/99
R/D initialed by: P. Cooney

APPEARS THIS WAY ON ORIGINAL

Filename, d:\nda\21-079r1.DOC

L. 06

REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA

AUG 13 1999

September 10, 1999

A. 1. NDA 21-079

SPONSOR Santen Incorporated
555 Gateway Drive
Napa, California 94558

2. PRODUCT NAMES: Pemirolast Potassium Ophthalmic Solution, 0.1% (Alamast™)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Ophthalmic solution of 10 mL 10 mL

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Inhibitor of Type I immediate *in vivo* hypersensitivity

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: March 25, 1999

2. DATE OF AMENDMENT: July 15, 1999 (subject of this review)

3. ASSIGNED FOR REVIEW: April 7, 1999

4. RELATED DOCUMENTS: DMF (DMF and IND

C. REMARKS: Microbiologist's Review #1 resulted in an Approvable recommendation with 4 deficiencies and a comment. The applicant replies to these questions in his

July 15, 1999 amendment, and this is the subject of the current review.

D. CONCLUSIONS: The submission is approvable upon resolution of the deficiencies noted in the "Microbiologist's Draft of List of Deficiencies."

/S/ 9-10-99

David Hussong, Ph.D.

/S/ 9/15/99

cc:

HFD 160/Consult File
HFD 550/R. Rodriguez/CSO
HFD 550/Chemist/R. Uppoor/L. Ng
HFD 805/D. Hussong

Drafted by: D. Hussong, 09/08/99
R/D initialed by: P. Cooney

Filename, d:\nda\21-079r2.DOC

7/20/99

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-079 SUBMISSION DATE: 3/25/99

NDA TYPE: 1P

PRODUCT: Alamast™
(Pemirolast potassium ophthalmic solution, 0.1%)

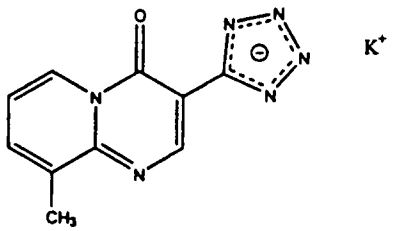
SPONSOR: Santen Incorporated REVIEWER: Veneeta Tandon, Ph.D.

NDA Review of a New Molecular Entity

I. BACKGROUND

Indication Pemirolast potassium ophthalmic solution, 0.1% is to be used for the prevention and relief of ocular itching due to allergic conjunctivitis in adults and children 3 years and older.

Dose and administration Four times daily for up to four months



Allergic conjunctivitis and vernal conjunctivitis are allergic diseases caused by antigens, such as various pollens, mites and house dust. The pathophysiological response in allergic conjunctivitis is initiated by the release of mediators from the inflammatory cells and the mast cells. Generally these diseases are treated by symptomatic therapy with corticosteroids. Lately disodium chromoglycate ophthalmic solution has been widely used as antiallergenic ophthalmic solutions, which inhibits release of chemical mediators from mast cells.

I agree VS 7/1/99

Pemirolast potassium is also a mast cell stabilizer that inhibits the in vivo Type I immediate hypersensitivity reaction. In vitro and in vivo studies have demonstrated that pemirolast potassium inhibits antigen-induced release of inflammatory mediators, such as, histamine, leukotriene C_4, D_4 and E_4 from human mast cells. In addition, it also inhibits the chemotaxis of eosinophils into ocular tissue and blocks the activation and release of mediators from human eosinophils. Although, the precise mechanism of action

is not known, pemirolast potassium has been reported to suppress the release of arachidonic acid, 1,2-diacetyl glycerol and inositol triphosphate.

Foreign Marketing History The formulation that is to-be-marketed in U.S. is approved in Japan, China and Korea for allergic and vernal conjunctivitis in adults and children since 1995, 1996 and 1998 respectively. 5 mg and 10 mg tablets have been approved for bronchial asthma and allergic rhinitis in adults and children five years of age and older in Japan since 1991. A non-alcoholic syrup formulation has been approved in Japan since 1992 for bronchial asthma in children over a year old. This will be the first mast cell stabilizer for allergic conjunctivitis to be approved in the U.S.

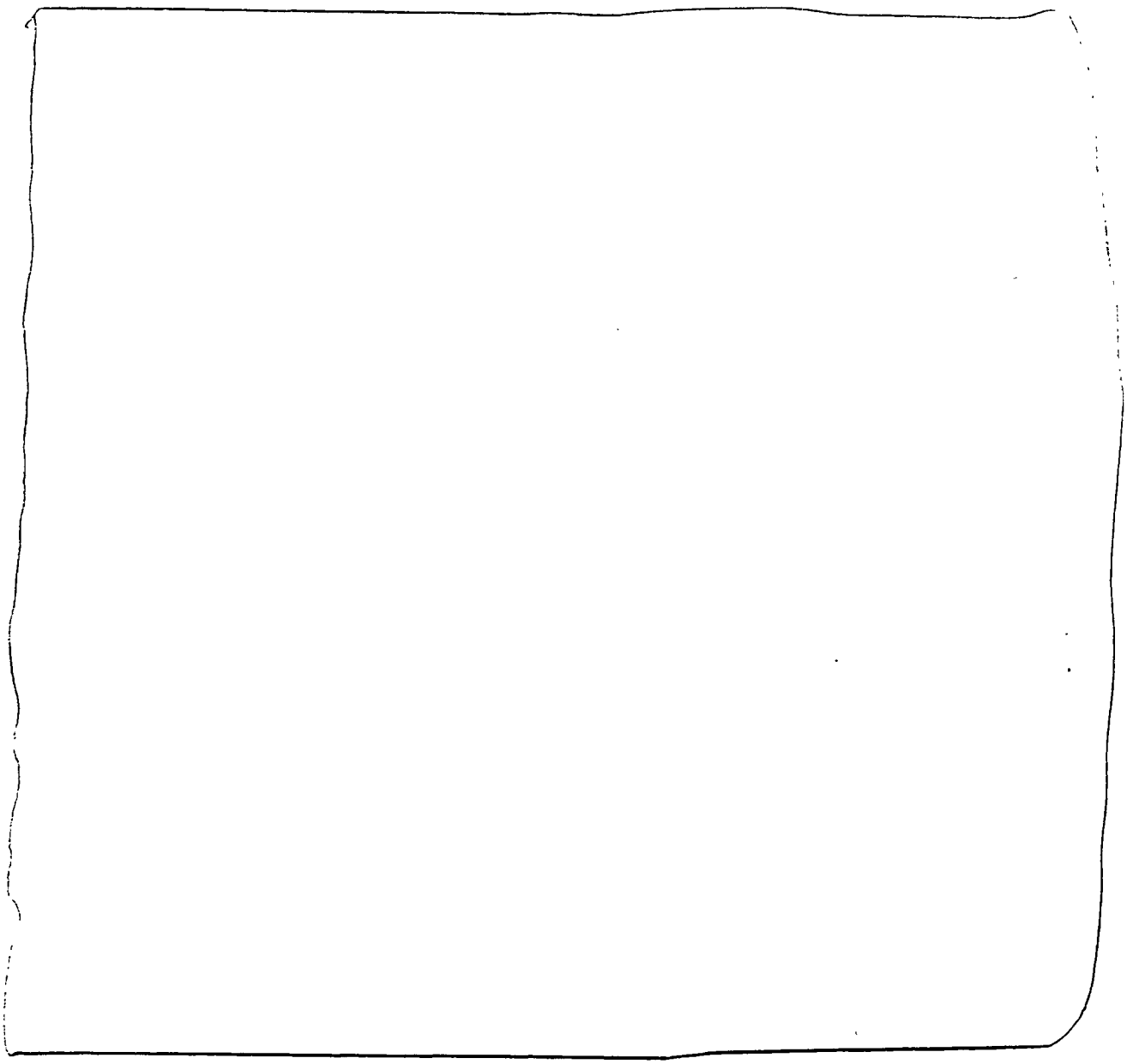
II. Recommendation

The reviewer recommends approval of the application from the standpoint of Clinical Pharmacology and Biopharmaceutics. Comment 1 and 2 on page 11 should be provided to the Sponsor for future submissions. Labeling Comments should be incorporated.

INDEX

III. FORMULATION

Ingredient	Quantity (mg/ml)	Percent (w/v)
Pemirolast potassium		
Lauralkonium chloride		
Glycerine		
Dibasic sodium phosphate		
Monobasic sodium phosphate		
Sodium hydroxide		
Phosphoric acid		
Purified water		



V. PHARMACOKINETIC STUDIES

The Clinical Pharmacokinetics section includes two studies to evaluate systemic absorption of 0.1% pemirolast potassium ophthalmic solution after topical administration. A couple of studies with oral administration of pemirolast were also provided. These studies are discussed in the following sub-sections.

(A) Topical Administration

- *Study 02-006* — *A two-week, open label study of drug plasma concentration following administration of 0.1% pemirolast potassium ophthalmic solution q.i.d. in normal healthy volunteers.*

The objective of this study was to evaluate systemic absorption of pemirolast potassium following single administration and repeat doses of 0.1% pemirolast potassium ophthalmic solution (lot # TC0637) for 14 days in both the eyes (1-2 drops). It was an open label, single center study in 16 (8M and 8F) healthy subjects (22-45 years, mean age 27 years). This population included 6 Caucasians, 1 Black and 9 Hispanics.

Plasma levels

Plasma samples were taken on Day 1, Day 7 ± 1 and Day 16 ±1, at predose, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose, relative to the first dose of the day. On Day 16, no additional doses were administered after the first morning dose. Plasma concentrations were measurable in all subjects for 8 hours. The pharmacokinetic parameters (mean ± SE) on each of the three days are provided in the following Table.

Day	$AUC_{0\text{-last}}$ (ng.hr/ml)	$AUC_{0\text{-}\infty}$ (ng.hr/ml)	T_{max} (hr)	C_{max} (ng/ml)	$t_{1/2}$ (hr)	λ_z (1/hr)
1	16.59 ± 1.97	22.62 ± 2.60	0.33 ± 0.03	4.09 ± 0.46	4.31 ± 0.23	0.017 ± 0.01
7 ± 1	21.12 ± 2.32	29.21 ± 3.39	0.39 ± 0.05	4.85 ± 0.05	4.23 ± 0.020	0.017 ± 0.01
16 ±1	20.52 ± 3.58	29.10 ± 5.23	0.42 ± 0.05	4.69 ± 0.75	4.51 ± 0.19	0.016 ± 0.01

Both λ_z and $t_{1/2}$ were unchanged during the course of the study, indicating that elimination of the drug was unaffected by repeated doses. There was a slight trend for C_{max} and T_{max} to increase with repeated dosing; however, these differences were not statistically significant ($p>0.3622$). For $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$, the Day 1 mean values, determined after a single dose of pemirolast, appeared to be smaller than the values determined for Days 7 and 16, which followed repeated dosing. Again, these differences were not statistically significant ($p>0.237$). This suggests that steady state was achieved by Day 7. However, to determine if there was a trend for the AUCs to increase with repeated dosing, individual plasma concentration-time data were reviewed. The data demonstrated that there was noticeable variability in the plasma concentrations obtained from a given subject on the three days of sampling. Some subjects demonstrated relatively consistent plasma concentration-time curves for pemirolast at all three visits. Other subjects had much higher plasma concentrations at one or two visits (e.g. subjects 1401, 1412 and 1414 has higher values on Day 1); however, the higher concentrations were not always observed after repeated dosing. The individual subject pharmacokinetic parameters for the three visits are attached in the Appendix on pages 14-16. The plasma concentration profile is also attached in the Appendix on page 17.

Reviewer's Comment

The variability seen on Days 1, 7 and 16 is not unusual in ophthalmic studies. In this study, the subjects were asked to administer one or two drops in each eye. This implies that each subject did not get the same dose and the same individual also did not get the same dose on each of the three visits. The actual number of drops administered was not recorded, hence dose normalization could not be done. In topical ophthalmic preparations as such there is a lot of variability in dosing due to drainage of the drug

product from the cul-de-sac of the eye or due to differences in drop volumes. Furthermore the flexible dosing schedule (1-2 drops) made evaluation of the resulting pharmacokinetic data difficult.

Pemirolast metabolite (TBX-01) concentrations in plasma were below the quantitative limits (0.05 ng/ml) at all sampling times in all but two subjects. In these two subjects the highest measurable metabolite concentration was 0.084 ng/mL.

Conclusions

- Pemirolast administered as 0.1% pemirolast potassium ophthalmic solution has consistent pharmacokinetics following single and repeat doses.
- Elimination of drug is not affected by repeat dosing and there is no significant accumulation in plasma with q.i.d. dosing for 14 days.

- *Study SR 2035* *A phase I clinical study of an antiallergic ophthalmic drug in healthy adults using 0.05%, 0.1% and 0.5% pemirolast potassium ophthalmic solution.*

The safety and pharmacokinetics of pemirolast potassium ophthalmic solution was investigated in 5 healthy adults (27-37 years, mean age 33.4 years) in a single-day trial and in 6 males (27-37 years, mean age 33.2 years) after a continuous week long administration. An escalation regimen was employed in the single-day trial, with each subject receiving 0.05% q.i.d., then 0.1% q.i.d. and finally 0.5% q.i.d. each for one day. There was a washout period between dosing days. The continuous week-long trial was conducted using 0.5% pemirolast potassium ophthalmic solution q.i.d. Plasma levels were not assessed at 0.05% q.i.d. regimen of pemirolast potassium solution, but safety was evaluated before increasing the dose. The single-day administration and multiple-day administration parts of this study will be discussed separately in the following sub-sections.

- *Single-day administration* (0.05, 0.1 and 0.5% dose levels q.i.d.)

Two drops of pemirolast potassium ophthalmic solution (0.05, 0.1 and 0.5%) was administered to each subject four times a day (0800, 1200, 1700 and 2200) in the left eye only, with the right eye serving as the untreated control.

Plasma levels

Blood was collected shortly before the second administration (1200) and at 1, 2, 3 hours after the second administration for the 0.1% or 0.5% pemirolast potassium ophthalmic solution.

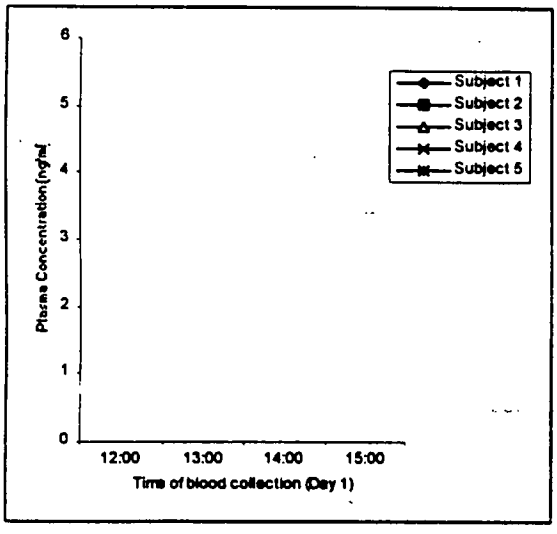
Blood samples collected for pharmacokinetics were processed for plasma and assayed for pemirolast concentrations using a [redacted] detection with a [redacted] Urine samples were treated

with glucuronidase to cleave any glucuronide metabolites of pemirolast and then assayed for pemirolast concentration using a [redacted] detection with a [redacted]

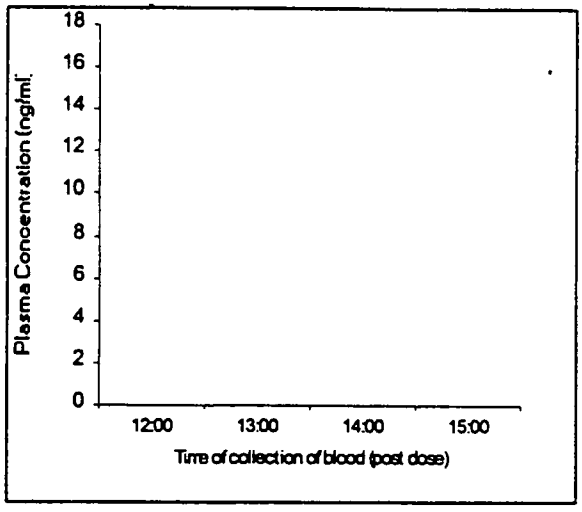
The mean ± SE of the plasma levels for the 0.1% and 0.5% regimen is shown below.

Time relative to 2nd dose (1200)	With 0.1% pemirolast solution	With 0.5% pemirolast solution
Pre-dose	1.6 ± 0.1 ng/ml	4.9 ± 1.1 ng/ml
1 hour post-dose	2.8 ± 0.7 ng/ml	9.7 ± 2.2 ng/ml
2 hours post-dose	2.5 ± 0.5 ng/ml	8.0 ± 1.8 ng/ml
3 hours post-dose	2.2 ± 0.4 ng/ml	6.7 ±1.6 ng/ml

The maximum plasma level was reached 1 hour after the administration of the dose followed by a slow decrease. The plasma concentration profiles of the 5 subjects dosed with 0.1% and 0.5% pemirolast potassium ophthalmic solution is given below (figures A and B). Blood samples were collected after the second dose. Please note the y-axis for the differences in the plasma levels between the two doses. The same subjects (3 and 5) have higher plasma levels with each of the doses.



(A) 0.1% pemirolast potassium solution



(B) 0.5% pemirolast potassium solution

According to the calculations based on average blood concentration, pemirolast half-life was 5.7 hours with 0.1% ophthalmic solution and 3.7 hours with 0.5% ophthalmic solution. Due to the limited number of sampling times and the short time interval until the next dose was administered, this is an estimation of the half-life and not a formal calculation.

Urinary excretion

Urine was collected before administration of 0.1% and 0.5% pemirolast potassium ophthalmic solution and 2 samples of 24 hour urine were collected after the first administration and on the day following the completion of administration.

The urinary pemirolast excretion is shown in the following table.

Pemirolast Concentration	Time	Excretion (μg)	% of dose* (mean ± S.E.)
0.1%	Day of instillation	52.4 ± 19.6	15.3 ± 5.7
	Day following instillation	blq	blq
0.5%	Day of instillation	164.1 ± 53.3	9.6% ± 3.1
	Day following instillation	28.7 ± 3.9	1.7 ± 0.2

*% dose was calculated by the following formulas
For 0.1%: % of dose/day = [excretion/one ad dose (342.8 μg as pemirolast)]x100
For 0.5%: % of dose/day = [excretion/one ad dose (1713.9 μg as pemirolast)]x100

The individual subject data for the two dose levels is attached in the Appendix on page 18.

- *Multiple-day administration* (0.5% dose level q.i.d. x 7)

Two drops of pemirolast potassium ophthalmic solution (0.5%) was administered to each subject four times a day (0800, 1200, 1700 and 2200) in the left eye only for a week, with the right eye serving as the untreated control.

Plasma levels

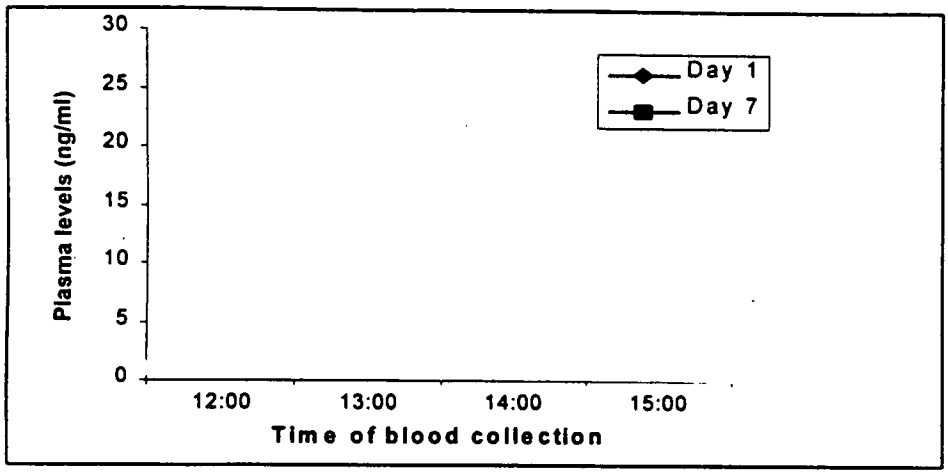
Blood was collected shortly before the second administration (1200), at 1300 and 1500, and shortly before the third administration (1700) on Days 1 and 7 (the final day administration), and 1 hour after the second administration (1300) on Days 3 and 5. To investigate accumulation, the blood was also taken after 11 hours and after 35 hours following the final administration.

Plasma levels 1 hour after the administration on Days 1, 3, 5 and 7 are shown in the following table.

1 hour post dose on Day	0.5% pemirolast solution
1[a]	14.8 ± 4.1 ng/ml
3	9.5 ±1.9 ng/ml
5	12.1 ± 3.1 ng/ml
7[a]	17.3 ± 4.2 ng/ml
8[b]	3.7 ± 0.6 ng/ml
9[b]	BLQ (1.0 ng/ml)

[a]Blood levels were also taken at 3 and 5 hours post dose on Days 1 and 7,only 1 hour post-dose mean is reported in this table.
[b]after 1 and 2 days of the completion of final administration (i.e at Day 7)

The plasma concentration profile on Day 1 and Day 7 are shown in the following figure.



According to calculations based on average blood concentration level, pemirolast half-life was 3.4 hours on Day 1 and 3.5 hours on Day 7. Due to the limited number of sampling times and the short time interval until the next dose was administered, this is an estimation of the half-life and not a formal calculation.

Urinary excretion

24-hour urine was collected before the administration and on Days 1, 4, and 7 of the treatment regimen. To investigate accumulation 24-hour urine was collected for 2 days following the completion of the administration.

The urinary excretion of pemirolast is shown the following table. The individual subject data is provided in the Appendix on page 18.

Time	Excretion (μg)	% of dose* (mean ± S.E.)
Day before instillation	blq	blq
Day 1	235 ±51.5	13.7 ±3.0
Day 4	205.3 ± 50.1	12.0 ±2.9
Day of completion of instillation	286 ± 54.0	16.7 ± 3.1
Day following completion of instillation	54.5 ± 8.6	3.2 ± 0.5
Two days after completion of instillation**	blq	blq

*% dose was calculated by the following formulas

% of dose/day = [excretion/one ad dose (1713.9 μg as pemirolast)] x100

** only one person had a levels of 14.2 μg

Reviewer's Comment

In Study 02-006, the mean C_{max} at Day 1 after the first dose (first after the q.i.d regimen) was 4.09±0.46 ng/ml at 0.33 ± 0.03 hours. In this study (SR 2035,) the mean plasma levels of pemirolast relative to the second dose on Day 1 is 2.8 ±0.7 ng/ml at 1 hour post-dose. Plasma levels form Study 02-006, continuously decreased after 0.5 hours, with mean plasma levels being 3.4 ± 0.46 ng/ml at 1 hours post dose on Day 1. This showed consistent results between the two studies after the administration of 0.1% pemirolast potassium ophthalmic solution to healthy subjects.

Conclusion

- Pemirolast ophthalmic solution 0.1% and 0.5% reaches the blood stream rapidly and also appears to be rapidly eliminated. Urinary excretion accounts for 10-15% of the administered by ophthalmic route.
- Pemirolast administered as 0.5% ophthalmic solution b.i.d. does not accumulate in plasma. The urinary excretion is also unaltered during a one-week course of treatment.

(B) Oral Administration

A couple oral studies will be briefly discussed here, mainly for the purpose of comparison between the levels obtained on topical dosing versus that obtained on oral dosing. These studies were not conducted for this submission (NDA 21-079), but were conducted during the development of tablets in Japan for the treatment of bronchial asthma and allergic rhinitis.

- <u>Study SR2032-P</u> *Plasma levels and urinary excretion in humans after administration of single and multiple oral doses of pemirolast in a tablet form.*

2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg doses were used in this study for single doses of pemirolast. For the multiple administration portion of the study, multiple doses of 10 mg t.i.d. were administered for 7 days. Blood and urine samples were collected for 24 hours post-dose. The limit of detection was 4 ng/ml in the plasma and 5 ng/ml in the urine.

Plasma Levels

Peak concentrations in plasma and AUC were proportional to dose after single dose administration, indicating no apparent change in first order absorption processes across the dose levels evaluated. k_e and $t_{1/2}$ were virtually constant over the dose range tested, indicating dose-independent kinetics; $t_{1/2}$ was four to five hours for all dose levels. The mean AUC (± SEM) was 1.463 ± 0.129 μg.hr/ml for the 2.5 mg single dose and 20.809 ± 1.770 μg.hr/ml for the 40 mg single dose. The mean Cmax (± SEM) was 0.231 ± 0.015 μg/ml for the 2.5 mg single dose and 3.648 ± 0.327 μg/ml for the 40 mg dose.

The multiple administration plasma results indicated no statistically significant changes in plasma concentrations with repeated doses, with C_{min} ranging from 0.245 to 0.362 µg/ml. Steady state was apparently reached by Day 2 of administration.

Urinary excretion

Urinary excretion in the single administration portion of the study was almost complete within 8 to 10 hours following oral administration. Only 0.6 to 2.4% of the total dose was excreted as pemirolast, the parent compound. Four metabolites were identified in urine, for total urinary excretion of 83 to 90% of the dose within 12 hours of a single pemirolast administration. The major metabolite (Glucoronidation of the parent compound TBX-02) accounted for 76-81% of the dose. The next most prevalent compound in the urine was 9-hydroxymethyl pemirolast (TBX-01) that accounted for about 5-8% of the dose. Two other glucoronide metabolites could not be identified due to extremely small amounts available. The dose administered did not affect the percentage of dose eliminated in various forms. Very low concentrations of TBX-02 and TBX-01 were present in the plasma. The levels have not been given in the report.

Urinary excretion after multiple doses remained almost constant. Total urinary excretion of pemirolast accounted for 1.3% of the total dose. Total urinary excretion of metabolites over 8 days accounted for 82.6% of the total dose administered. Urinary excretion was essentially the same after single and multiple doses of pemirolast.

Pharmacokinetic parameters and plasma concentration profiles after single and multiple doses are attached in the Appendix on page 19-20.

Reviewer's Comment

- *The sponsor has not measured the urinary excretion of the metabolites (TBX-01 and TBX-02) after topical ocular administration, but has measured the metabolite TBX-01 in plasma. From the oral study the sponsor knew that the plasma levels of the metabolites are low. TBX-02 appears in larger concentrations in the urine. Its concentration in the plasma is higher than TBX-01.*
- *The sponsor has measured the urinary excretion of the parent compound. A higher percentage (10-15% of the dose) appears to be excreted in the urine as parent compound after topical administration, as compared to 0.6-2.4% of the dose after oral administration. Plasma levels and cumulative urinary excretion of the parent compound, TBX-01 and TBX-02 after oral administration is provided in the Appendix on page 21-22.*
- *The activities of these metabolites have not been mentioned.*

(C) Plasma Protein Binding

Plasma protein binding of pemirolast was assessed in vitro using micropartition centrifugal protein binding system. Protein binding to serum albumin and α_1-acid glycoprotein was also evaluated in order to determine which protein(s) bind pemirolast.

Plasma protein binding was 96% in human plasma in the concentration range of 0.1 to 2.5 μg/ml. Binding to serum albumin was the same as that of human plasma, suggesting the binding protein for pemirolast is albumin.

(D) Other Studies

There was another study of pemirolast non-alcoholic syrup in children with bronchial asthma and a drug interaction study with theophylline. These two studies pertain to the use of pemirolast in the treatment of asthma and would not impart any additional knowledge for pemirolast potassium ophthalmic solution intended to be used for the treatment of allergic conjunctivitis. Hence, these studies were not thoroughly reviewed. In brief, the pemirolast pharmacokinetics were essentially the same in children with bronchial asthma and the healthy adult subjects. However, only the summary reports of these studies were submitted, hence the adequacy of these studies cannot be defined at this time. There were no statistically significant differences in the pharmacokinetic parameters of theophylline when co-administered with pemirolast, except for T_{max}, which increased from 3.7 to 6.3 hours. Theophylline did not alter the pharmacokinetics of pemirolast.

VI. OVERALL CONCLUSIONS

- The systemic absorption of 0.1% pemirolast potassium ophthalmic solution has been evaluated in healthy subjects with asymptomatic eyes.
- Pemirolast administered as 0.1% pemirolast potassium ophthalmic solution has consistent pharmacokinetics following single and repeat doses.
- Elimination of drug is not affected by repeat dosing and there is no significant accumulation in plasma with q.i.d. dosing for 14 days.
- Pemirolast levels in the plasma are 65 to 140 folds lower after topical administration of 0.1% ophthalmic solution (1 mg/ml), as compared to single oral doses of 2.5 mg to 40 mg in a Japanese population.

VII. COMMENTS

1. Disease conditions that are associated with ocular inflammation have been shown to increase ocular absorption as compared to healthy eyes. For future drug development, the sponsor is encouraged to evaluate systemic absorption in patients rather than healthy volunteers.
2. For future submissions, the sponsor is encouraged to provide proper tabs indicating each discipline/section (e.g Chemistry, Nonclinical pharmacology etc.) in the overall summary of the NDA as submitted in Volume 1.1 of application.

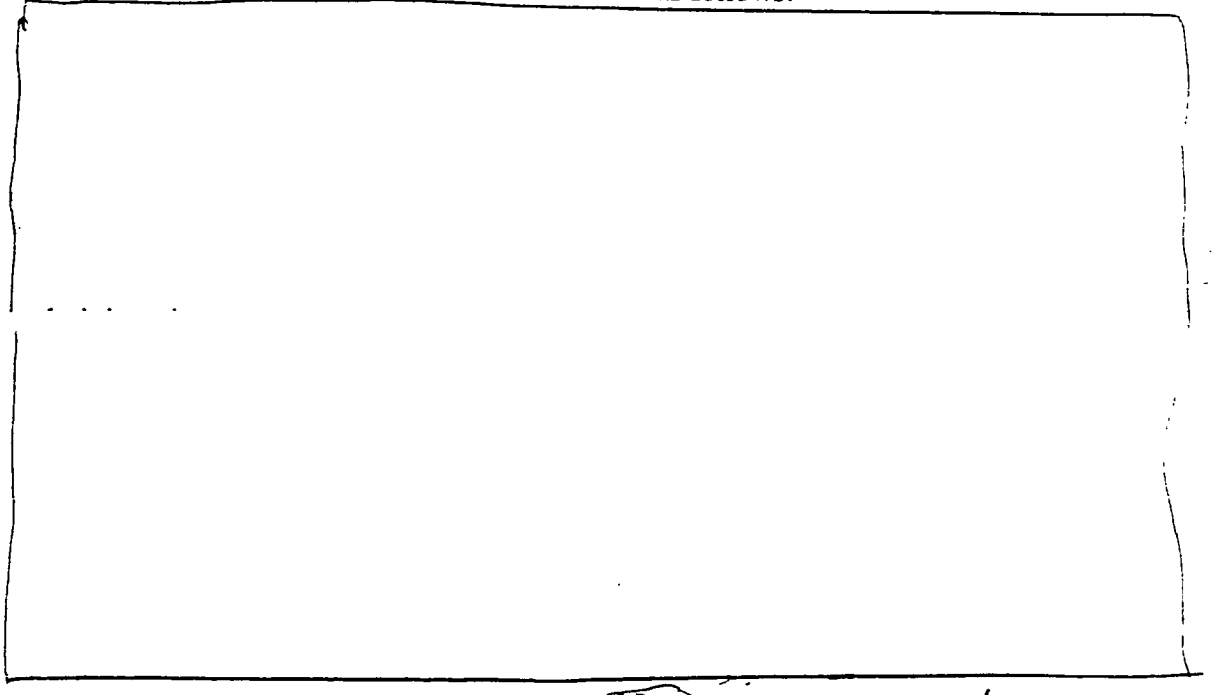
VIII. LABELING

In the "CLINICAL PHARAMCOLOGY"section of the Label, the separate subheading "*Pharmacokinetics*" should be included. This subsection should be separated from the "*Mechanism of action*" subsection within the section (which would include the first four

paragraphs in this section). The references of these are provided in the NonClinical Pharmacology section of the NDA and will be reviewed by the Pharmacologist.

The *"Pharmacokinetics"* subsection should begin with description of the pharmacokinetics after topical administration and should then include the sections on oral administration.

The *"Pharmacokinetics"* subsection should read as follows:



/S/ 7/14/99

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. /S/ 7/14/99

CC: NDA 21-079
HFD-550/Div File
HFD-550/CSO/Rodriguiz
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPENDIX
NDA 21-079

Table 6.3: Analytical Methods Employed in *In Vivo* Biopharmaceutics Studies of Pemirolast

Study Number	Type of Biological Fluid	Method	Sensitivity of Method/ Range	Specificity (parent/metabolites)
02-006	Plasma			
SR2035	Plasma			
SR2035	Urine			
SR2032-P & 90006	Plasma			
SR2032-P & 90006	Urine			
90015	Plasma			
90015	Urine			
94024	Plasma			

Table 15.3.1
Summary of Pharmacokinetic Parameters
Santen Protocol: 02-006

Visit	Subject	$AUC_{0-t_{last}}$ (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T_{max} (hours)	C_{max} (ng/mL)	$t_{1/2}$ (hours)	λ_z
1	1401						
1	1402						
1	1403						
1	1404						
1	1405						
1	1406						
1	1407						
1	1408						
1	1409						
1	1410						
1	1411						
1	1412						
1	1413						
1	1414						
1	1415						
1	1416						
	N	16	16	16	16	16	16
	Mean	16.59	22.62	0.33	4.09	4.31	0.17
	SE	1.97	2.60	0.03	0.46	0.23	0.01
	Min						
	Median	12.99	18.07	0.25	3.21	4.15	0.17
	Max						

APPEARS THIS WAY
ON ORIGINAL

Table 15.3.1
Summary of Pharmacokinetic Parameters
Santen Protocol: 02-006

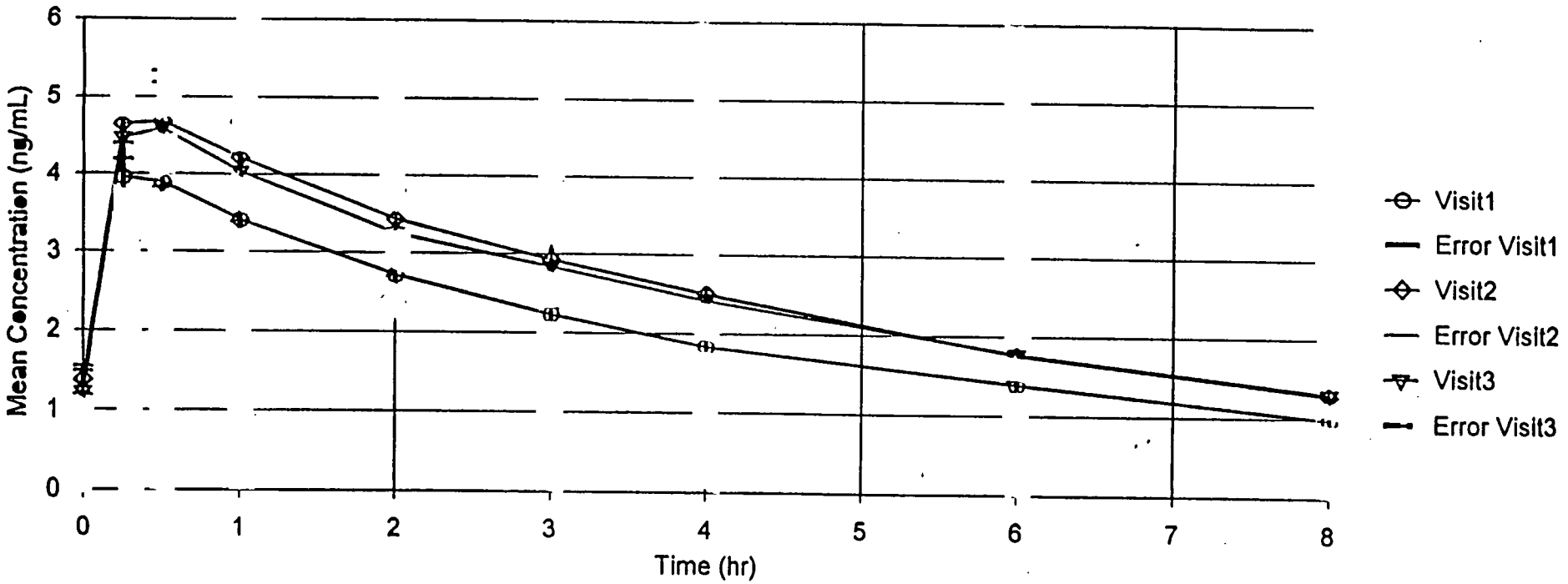
Visit	Subject	AUC_{0-hour} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T_{max} (hours)	C_{max} (ng/mL)	$t_{1/2}$ (hours)	λ_z
2	1401						
2	1402						
2	1403						
2	1404						
2	1405						
2	1406						
2	1407						
2	1408						
2	1409						
2	1410						
2	1411						
2	1412						
2	1413						
2	1414						
2	1415						
2	1416						
	N	16	16	16	16	16	16
	Mean	21.12	29.21	0.39	4.85	4.23	0.17
	SE	2.32	3.39	0.05	0.50	0.20	0.01
	Min						
	Median	21.72	30.50	0.25	5.01	4.33	0.16
	Max						

APPEARS THIS WAY
ON ORIGINAL

Table 15.3.1
Summary of Pharmacokinetic Parameters
Santen Protocol: 02-006

Visit	Subject	$AUC_{0-t_{last}}$ (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T_{max} (hours)	C_{max} (ng/mL)	$t_{1/2}$ (hours)	λ_z
3	1401						
3	1402						
3	1403						
3	1404						
3	1405						
3	1406						
3	1407						
3	1408						
3	1409						
3	1410						
3	1411						
3	1412						
3	1413						
3	1414						
3	1415						
3	1416						
	N	16	16	16	16	16	16
	Mean	20.52	29.10	0.42	4.69	4.51	0.16
	SE	3.58	5.23	0.05	0.75	0.19	0.01
	Min						
	Median	15.74	21.31	0.50	3.79	4.56	0.15
	Max						

Figure 15.3.2
Plot of Mean Pemirolast Concentrations



BQL values are not shown in the plot, but are included in PK calculations.

(A) SINGLE DAY ADMINISTRATION

2 Pharmacokinetic Parameters

2.1 Blood and urinary concentration of TB

Day	Time	Blood concentration (ng/mL)					Urinary concentration (μg)				
Patient #		1	2	3	4	5	1	2	3	4	5
Before admin.											
Day 4	12:00										
	13:00										
	14:00										
	15:00										
Day 5	16:00										
Day 8	12:00										
	13:00										
	14:00										
	15:00										
Day 9											

Test drug: Day 4 - 0.1% TBX, Day 8 - 0.5% TBX

N/A: Not applicable, B.D.: Below detection limit

(B) MULTIPLE DAY ADMINISTRATION

2 Pharmacokinetic Parameters

2.1 Blood and urinary concentration of TB (1 Week Administration)

Day	Time	Blood concentration (ng/mL)						Urinary concentration (μg)					
Patient #		1	2	3	4	5	6	1	2	3	4	5	6
Before admin.													
Day 1 (Jan 12)	12:00												
	13:00												
	15:00												
	17:00												
Day 3 (Jan. 14)													
Day 4 (Jan. 15)													
Day 5 (Jan. 16)													
Day 7 (Jan. 18)	12:00												
	13:00												
	15:00												
	17:00												
Day 8 (Jan. 19)													
Day 9 (Jan. 20)													

N/A: Not applicat

Table 1: Pharmacokinetic parameters in humans after single oral administration of TBX tablets

Parameter	Dose (mg/body) 2.5	5	10	20	40
K_a (hr^{-1})	0.631[a)]	0.494[b)]	0.686±0.370	0.412[a)]	1.22±0.649
K_e (hr^{-1})	0.142±0.015	0.163±0.013	0.151±0.019	0.163±0.008	0.174±0.009
$t_{1/2}$ (hr)	4.99±0.53	4.31±0.31	4.74±0.58	4.26±0.20	4.00±0.23
T_{max} (hr)	1.2±0.4	1.0±0.5	1.7±0.3	1.0±0.5	1.3±0.33
C_{max} (μg/mL)	0.231±0.015	0.416±0.071	0.723±0.021	1.712±0.217	3.648±0.327
AUC(μg-hr/mL)	1.463±0.129	2.279±0.339	5.020±0.716	9.420±1.177	20.809±1.770

Values are the mean ± S.E. (n=3)
a) Mean (n=2)

Table 2: Cumulative urinary excretion of TBX in humans after a single oral administration of TBX tablets

Time (hr)	% of Dose 2.5 mg/body	5 mg/body	10 mg/body	20 mg/body	40 mg/body
0~2	0.5 ± 0.3	0.2 ± 0.1	0.3 ± 0.1	0.6 ± 0.3	0.1 ± 0.0
0~4	0.8 ± 0.4	0.4 ± 0.2	1.0 ± 0.5	1.5 ± 0.6	0.3 ± 0.1
0~6	0.9 ± 0.3	0.5 ± 0.3	1.3 ± 0.7	1.8 ± 0.6	0.4 ± 0.1
0~8	1.1 ± 0.4	0.7 ± 0.3	1.5 ± 0.8	2.1 ± 0.6	0.5 ± 0.1
0~10	1.3 ± 0.5	0.7 ± 0.3	1.6 ± 0.8	2.2 ± 0.6	0.5 ± 0.2
0~12	1.3 ± 0.5	0.8 ± 0.3	1.6 ± 0.8	2.3 ± 0.6	0.5 ± 0.2
0~24	1.5 ± 0.5	0.8 ± 0.3	1.7 ± 0.8	2.4 ± 0.6	0.6 ± 0.2

Values are the mean ± S.E. (n=3)

Table 3 : Urinary excretion of TBX in humans following oral administration of TBX tablets thrice a day for 7 days

Day	% of Dose
1~2	1.2 ± 0.7
2~3	1.3 ± 1.0
3~4	0.6 ± 0.2
4~5	1.0 ± 0.6
5~6	2.1 ± 1.4
6~7	1.2 ± 0.6
7~8	1.5 ± 0.5
1~8	1.3 ± 0.7

Values are the mean ± S.E. (n=3)

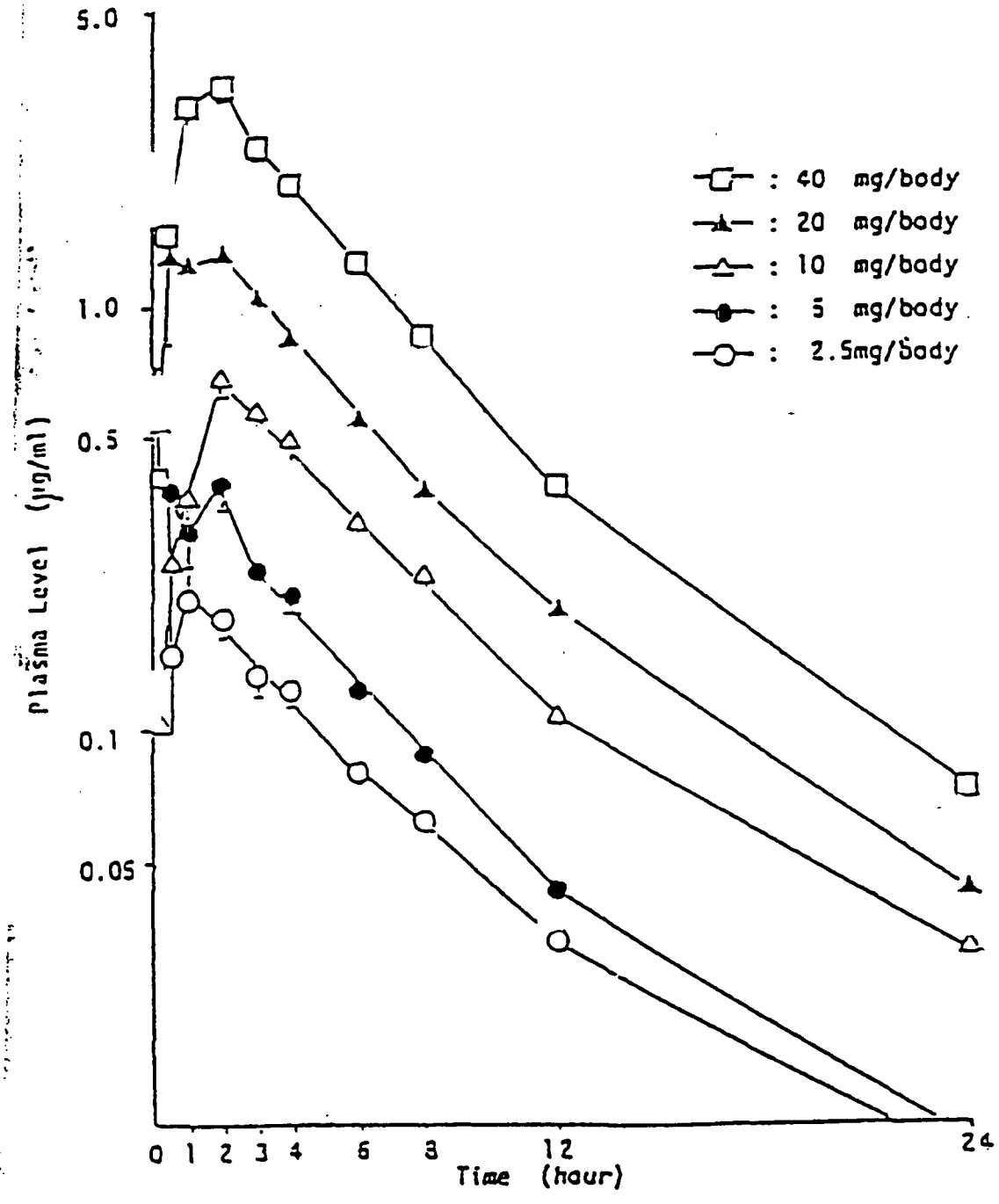


Figure 1: Plasma TBX levels in humans after single oral administration of TBX (Dose: 2.5, 5, 10, 20, 40 mg/body). Values are the mean ± S.E. (n=3)

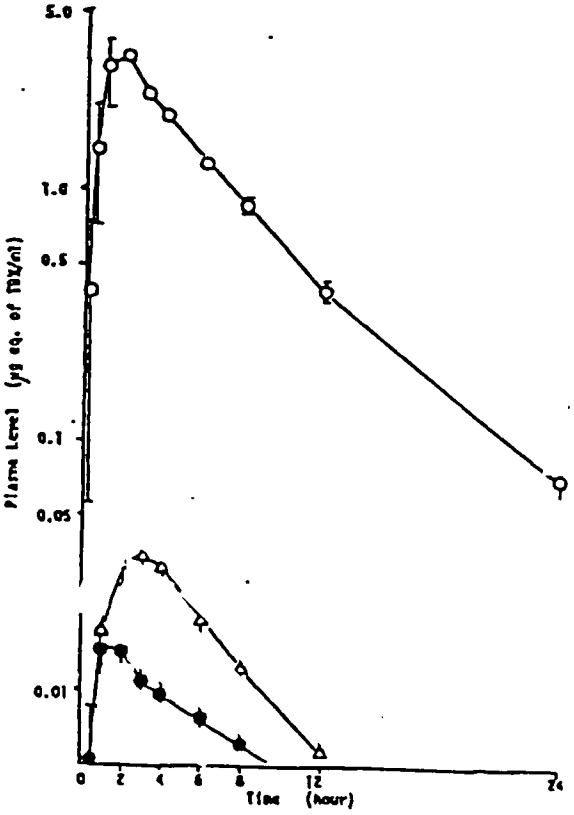


Fig. 4 Plasma levels of unchanged drug (○), TBX-01 (●) and TBX-02 (△) after an oral administration of TBX in human (Dose: 40 mg/body). Values are the mean±S.E. (n=3).

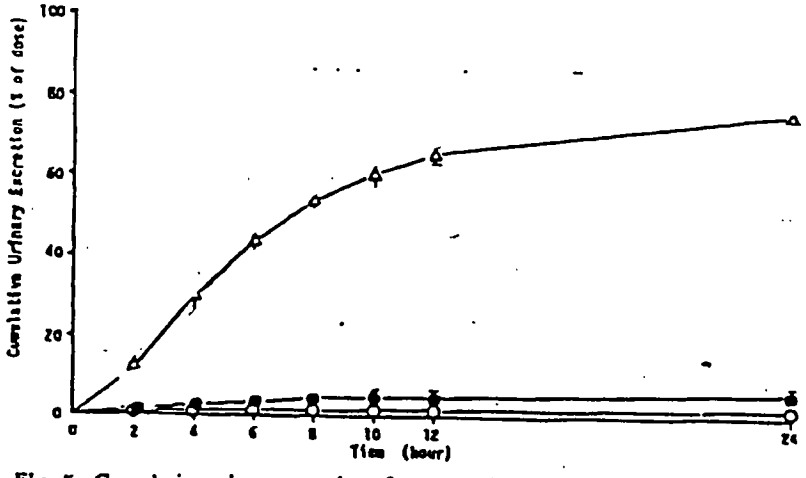


Fig. 5 Cumulative urinary excretion of unchanged drug (○), TBX-01 (●) and unchanged drug's glucuronide (△) after an oral administration of TBX in human (Dose: 10 mg/body). Values are the mean±S.E. (n=3).

3/25/99

Santen

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0.1% Pemirolast Potassium Ophthalmic Solution

(NDA 21-079)

ITEM 13 PATENT INFORMATION

Patent Number and Date of Expiration:

Patent # : 5,034,230
Expiry Date: 12/23/08

Type of Patent:

Drug Product (Anti-allergic ophthalmic solution)
Method of Use (Treating allergic eye diseases)

Name of Patent Holder:

Santen Pharmaceutical Co. Ltd.
Osaka, Japan

Name of U.S. representative authorized to receive notice of patent certification:

Michelle Veenstra, J.D.
Director, Regulatory Affairs
Santen Incorporated

Declaration:

The undersigned declares that Patent No. 5,034,230 covers the formulation, composition, and/or method of use for 0.1% pemirolast potassium ophthalmic solution. This product is the subject of this application for which approval is being sought.

Merwin Jerry Hansen
Chief Executive Officer
Santen Incorporated

3/17/99
Date

0100011

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0.1% Pemirolast Potassium Ophthalmic Solution

(NDA 21-079)

ITEM 14 PATENT CERTIFICATION

Paragraph II Certification:

Santen hereby certifies that in our opinion, and to the best of our knowledge, Patent No. 4,122,274, which covers the drug substance pemirolast potassium, has expired.

Merwin Jerry Hansen
Chief Executive Officer
Santen Incorporated

3/17/99
Date

United States Patent [19]

Morita et al.

[11] Patent Number: 5,034,230

[45] Date of Patent: Jul. 23, 1991

[54] ANTI-ALLERGIC OPHTHALMICS

[75] Inventors: Takakazu Morita, Toyonaka; Tadashi Iso, Kawachinagano; Youichi Kawashima, Kyoto; Mitsushi Hikida, Takatsuki, all of Japan

[73] Assignee: Santen Pharmaceutical Co., Ltd., Osaka, Japan

[21] Appl. No.: 392,922

[22] PCT Filed: Dec. 23, 1988

[86] PCT No.: PCT/JP88/01296

§ 371 Date: Jul. 28, 1989

§ 102(e) Date: Jul. 28, 1989

[87] PCT Pub. No.: WO89/06130

PCT Pub. Date: Jul. 13, 1989

[30] Foreign Application Priority Data

Dec. 25, 1987 [JP] Japan 62-331025

[51] Int. Cl.[5] A61F 2/00; A61K 9/08

[52] U.S. Cl. 424/427; 424/428; 424/659; 424/660; 514/914; 514/269

[58] Field of Search 514/269, 914; 424/427, 424/659, 660, 428

[56] References Cited

U.S. PATENT DOCUMENTS

4,122,274 10/1978 Juby 544/116

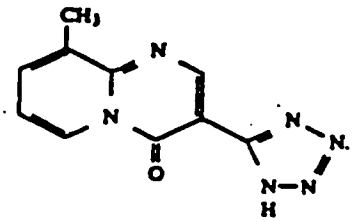
FOREIGN PATENT DOCUMENTS

60-50197 11/1985 Japan .

Primary Examiner—Thurman K. Page
Assistant Examiner—James M. Spear
Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

[57] ABSTRACT

This invention relates to low irritative ophthalmics containing the compound of the formula or salts thereof which are useful for treatment of anti-allergic eye diseases such as allergic conjunctivitis



[I]

22 Claims, No Drawings

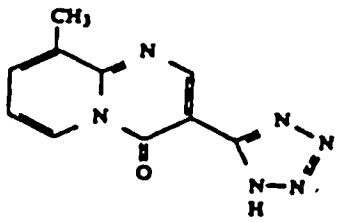
ANTI-ALLERGIC OPHTHALMICS

FIELD OF THE INVENTION

This invention offers ophthalmics which are useful for treatment of allergic eye diseases such as allergic conjunctivitis.

BACKGROUND OF THE INVENTION

Japanese Patent Publication (Publication No. Sho 60-50197) discloses that the compound of the formula [I] and salts thereof (hereinafter called as Compound [I]) are excellent anti-allergic drugs.



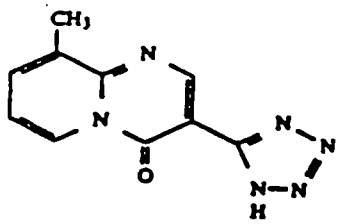
[I]

But, ophthalmic application of Compound [I] has not been studied, so, it is necessary to examine preparation methods of ophthalmic formulations and study the effect on allergic eye diseases.

As the result of our precise studies on preparation methods of ophthalmic formulations and the effect on allergic eye diseases, we found that Compound [I] has an excellent anti-allergic effect in eyes and has a possibility to be applied to stable and low irritative ophthalmics.

DISCLOSURE OF THE INVENTION

This invention relates to the anti-allergic ophthalmics containing the compound of the formula [I] or salts thereof (hereinafter called as Compound [I]) as a main ingredient.



[I]

Examples of the salts of the compound [I] are metal salts such as potassium, sodium, calcium and magnesium and organic amine salts.

Compound [I] is already known to have an excellent anti-allergic effect However, the application to ophthalmics and its effect on allergic eye diseases have not been known.

Topical diseases such as eye diseases are efficiently treated by topical application of a drug and it is necessary to study a topical application of oral drug to ophthalmics

Especially, the potassium salt of Compound[I], that is 9-methyl-3-(1H-tetrazole-5-yl)-4H-pyrido[1,2-a]pyrimidine-4-one potassium salt (hereinafter called as Compound A), is an excellent anti-allergic drug, so we studied mainly an application of the potassium salt to ophthalmics.

Important factors for ophthalmics are not only to have excellent efficacy, but also low irritation because ophthalmics are administered directly to the eye, which is a highly sensitive organ.

Particularly, patients with allergic diseases complain of a strong pain in the eye, so less irritative ophthalmics are desired to treat such patients

As the result of the experiment using eye drops of Compound A as one of the examples, the details of which are described later in the article of the irritation test, we found that the eye drops cause little eye irritation and the ophthalmics of this invention are well applicable to anti-allergic ophthalmics.

Furthermore, in the case of eye drops, stability in solution is required, which is different from an oral drug, because the ingredients should be dissolved. We examined the stability of the eye drops of compound A. As the result of a preservation test during 6 months in the condition at 40° C. and 75% of relative humidity, a notable change was not observed and the eye drops proved to have good stability.

These properties cannot be presumed from the properties of oral preparations and can be found only from the application study to ophthalmics.

We examined the efficacy of ophthalmics, which is the most important property, and found that Compound A showed strong anti-allergic effect by topical application, the details of which and described later in the disclosure of the pharmacological test using eye drops of Compound A, and the ophthalmics of this invention were very useful for treatment of allergic eye diseases, such as allergic conjunctivitis.

Furthermore, to apply a medical substance to eye drops, the solubility of the substance is an important factor.

If a substance is easily soluble in water, any particular consideration is not necessary.

But, if a medical substance is hardly soluble in water, or if a substance, once dissolved in water, is readily crystallized while storing, many kinds of studies are required to formulate such substance in eye drops.

Compound A, which is an excellent anti-allergic drug, is a water soluble substance, but, readily precipitates as crystals after being dissolved in water. So, such problem about soluability has to be solved to formulate Compound A in eye drops.

A method using a solubilizer such as polyvinyl alcohol is considered first. However, the problem mentioned above can not be solved and another idea is required. Furthermore, in the case of eye drops, when a concentration of potassium is raised, there is a fear of causing corneal damage. So, particular consideration is required to apply such substance to ophthalmics.

When dosage frequency is not high, the potassium concentration is not an important problem. But, when continuous administration of the ophthalmics is required to treat eye diseases, it is important to lower the potassium concentration.

As the result of our intensive studies to solve such problems, we found that the problems could be solved immediately by using a sodium phosphate buffer or borate buffer.

We found that especially superior eye drops could be prepared by using a combination of disodium hydrogen phosphate and sodium dihydrogen phosphate, disodium hydrogen phosphate and potassium dihydrogen phosphate, boric acid and sodium borate or boric acid and monoethanolamine.

The combination amount and ratio of the buffer depend on the concentration of Compound A, however, when the concentration of Compound A is 0.01–1%, the following are preferable combinations.

Disodium hydrogen phosphate and sodium dihydrogen phosphate are 0.1–2% and 0.002–1% respectively Disodium hydrogen phosphate and potassium dihydrogen phosphate are 0.1–1% and 0.002–0.7% respectively. Boric acid and sodium borate are 0.3–2% and 0.3–1% respectively. Boric acid and monoethanolamine are 0.3–2% and 0.1–1% respectively.

We explained eye drops of Compound A in detail. However, this invention should not be restricted to eye drops, but should include all dosage forms such as suspensions and eye ointments which can be administered topically. The ophthalmics can be prepared by combining additives required according to the dosage forms.

Examples of additives usually combined in ophthalmics are tonicity agents such as sodium chloride, potassium chloride and concentrated glycerin, stabilizers such as sodium sulfite and disodium edetate, preservatives such as benzalkonium chloride, surfactants such as polysorbate 80 and polyoxyethylene hydrogenated castor oil, pH adjusting agents such as sodium hydroxide, potassium hydroxide and hydrochloric acid and eye ointment bases such as vaseline and liquid paraffin.

The concentration of Compound [I] in ophthalmics can be defined in the range of effective dose, but preferably 0.01–1%.

The pH value of the ophthalmics of this invention can be adjusted according to the range acceptable in ophthalmics, but in eye drops of Compound A, the pH is preferably 7–9.

The typical preparation method of the ophthalmics of this invention is that Compound[I] is added to sterile purified water or an eye ointment base and formulated by adding a tonicity agent, buffering agent, stabilizer, preservatives, surfactant, pH adjusting agent, etc.

BEST MODE TO MAKE THE INVENTION

Example 1

Formulation A

Compound A	0.3 g
sodium dihydrogen phosphate	0.01 g
disodium hydrogen phosphate	0.35 g
concentrated glycerin	2.0 g
benzalkonium chloride	0.005 g
sterile purified water	q.s.
total	100 ml

Preparation method

Sodium dihydrogen phosphate, disodium hydrogen phosphate, concentrated glycerin and benzalkonium chloride were dissolved in 80 ml of sterile purified water and then Compound A was added to the solution. After dissolving Compound A, sterile purified water was added to adjust the total volume to 100 ml.

Eye drops of the formulation B–E were prepared by the similar method as Example 1.

Formulation B

Compound A	0.05 g
sodium dihydrogen phosphate	0.04 g
disodium hydrogen phosphate	1.4 g
potassium chloride	0.7 g
benzalkonium chloride	0.005 g
sterile purified water	q.s.
total	100 ml

Formulation C

Compound A	1.0 g
boric acid	1.8 g
monoethanolamine	0.6 g
sodium sulfite	0.2 g
benzalkonium chloride	0.005 g
sterile purified water	q.s.
total	100 ml

Formulation D

Compound A	0.01 g
boric acid	0.81 g
sodium borate	0.67 g
potassium chloride	0.24 g
benzalkonium chloride	0.005 g
sterile purified water	q.s.
total	100 ml

Formulation E

Compound A	0.1 g
sodium dihydrogen phosphate	0.008 g
disodium hydrogen phosphate	0.32 g
concentrated glycerin	1.8 g
benzalkonium chloride	0.005 g
sterile purified water	q.s.
total	100 ml

Example 2

Formulation F

Compound A	0.5 g
boric acid	0.7 g
sodium chloride	0.13 g
benzalkonium chloride	0.005 g
potassium hydroxide	q.s.
sterile purified water	q.s.
total	100 ml

Preparation method

Boric acid, sodium chloride and benzalkonium chloride were dissolved in 80 ml of sterile purified water. Compound A was added to the solution, pH was adjusted to 8.5 with potassium hydroxide and sterile purified water was added to the solution to adjust the total volume to 100ml

Eye drops of the formulations G–I were prepared by the similar method as Example 2.

Formulation G

Compound A	0.01 g
sodium dihydrogen phosphate	0.73 g
disodium hydrogen phosphate	0.71 g
benzalkonium chloride	0.005 g
potassium chloride	0.21 g

-continued

potassium hydroxide	q.s.
sterile purified water	q.s.
total	100 ml

Formulation H

Compound A	0.01 g
potassium dihydrogen phosphate	0.6 g
disodium hydrogen phosphate	0.3 g
benzalkonium chloride	0.01 g
potassium chloride	0.5 g
sodium hydroxide	q.s.
sterile purified water	q.s.
total	100 ml

Formulation I

Compound A	1.0 g
sodium dihydrogen phosphate	0.3 g
disodium hydrogen phosphate	0.15 g
concentrated glycerin	1.4 g
benzalkonium chloride	0.005 g
potassium hydroxide	q.s.
sterile purified water	q.s.
total	100 ml

PHARMACOLOGICAL TEST

The inhibition effect of an anaphylactic reaction is usually measured as an indication to examine an efficacy on allergic diseases.

We examined the inhibition effect of an anaphylactic reaction of ophthalmics of this invention, using a rat conjunctiva model in which a passive cutaneous anaphylactic reaction was induced. Sodium cromoglycate, which has been applied to anti-allergic ophthalmics, was used as a comparative drug.

Experimental Method

According to the method of ISO et. al. (Ophthalmic Res., 12, 9 (1980)), we examined the inhibition effects of test compounds on allergy of rat conjunctiva, using four times diluted antiserum (PCA titer 1:32) prepared by Mota's method (Life Sci., 12, 917 (1963)). Ten μl of eye drops, which was prepared by dissolving the test compound in saline and adjusted pH 7.5, was dropped 5 and 15 minutes before challenge of antigen.

Result

test compound	concentration (%)	inhibition effect of anaphylactic reaction (%)
Compound A	0.01	55.5
Compound A	0.1	88.5
Compound A	1.0	94.8
Sodium cromoglycate	2.0	9.5

The inhibition percent of the anaphylactic reaction of the eye drops of this invention is, even if the concentration of Compound A is low such as 0.01%, over 50%. In case of the eye drops containing 1.0% of Compound A, the inhibition percent was over 90%.

The anti-allergic effect of Compound A by topical application is superior to that of sodium cromoglycate.

The results prove the utility of the ophthalmics of this invention.

IRRITATION TEST

Measurement of blinking rate and Draze test using a rabbit are usually applied as the indicator to examine eye irritation caused by ophthalmics.

We examined the irritation, comparing the ophthalmics of this invention with its vehicle.

As one of the examples, the result using the ophthalmics of the Formulation I in Example 2 is shown below. Each blinking rate one minute after one drop application of the eye drops of the Formulation I or one drop of its vehicle is low, such as 0.8 times (mean value of 5 rabbits), and irritation by the medicament was not recognized.

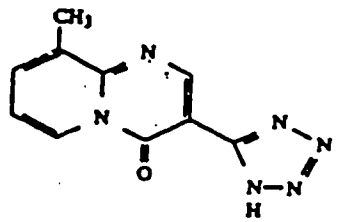
After 10 times applications of the eye drops of the Formulation I or its vehicle, we scored according to the improved Draze method (Fukui et. al., Gendai no Rinsyo 4, 277 (1970)) and found no damage in either case. The results showed that the irritation of the ophthalmics of this invention was weak.

UTILITY IN AN INDUSTRY

This invention provides low irritative ophthalmics which are useful for treatment of allergic eye diseases such as allergic conjunctivitis.

What we claim is:

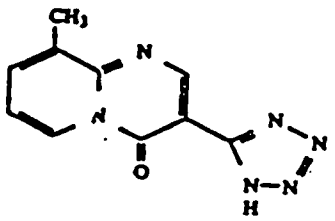
1. An anti-allergic ophthalmic solution comprising a potassium salt of a compound of the formula (I)



(I)

in a concentration from 0.01 to 1% and at least one buffer selected from the group consisting of disodium hydrogen phosphate, sodium dihydrogen phosphate, boric acid and sodium borate, either alone or in admixture with one or more pharmaceutically acceptable excipients.

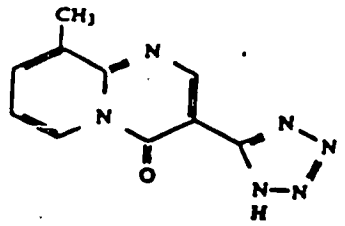
2. An anti-allergic ophthalmic solution comprising a potassium salt of a compound of the formula (I)



(I)

disodium hydrogen phosphate, sodium dihydrogen phosphate and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the potassium salt of the compound of the formula (I), the disodium hydrogen phosphate and the sodium dihydrogen phosphate are 0.01 to 1%, 0.1 to 2% and 0.002 to 1%, respectively.

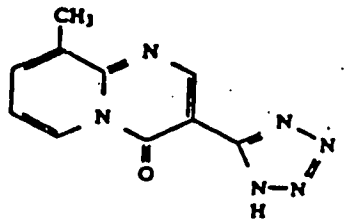
3. An anti-allergic ophthalmic solution comprising a potassium salt of a compound of the formula (I)



(I)

disodium hydrogen phosphate, potassium dihydrogen phosphate and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the potassium salt of the compound of the formula (I), the disodium hydrogen phosphate, and the potassium dihydrogen phosphate are 0.01 to 1%, 0.1 to 1% and 0.002 to 0.7%, respectively.

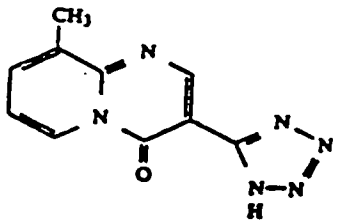
4. An anti-allergic ophthalmic solution comprising a potassium salt of a compound of the formula (I)



(I)

boric acid, sodium borate and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the potassium salt of the compound of the formula (I), the boric acid and the sodium borate are 0.01 to 1%, 0.3 to 2% and 0.3 to 1%, respectively.

5. An anti-allergic ophthalmic solution comprising a potassium salt of a compound of the formula (I)

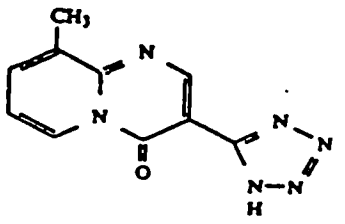


(I)

boric acid, monoethanolamine and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the potassium salt of the compound of the formula (I), the boric acid and the monoethanolamine are 0.01 to 1%, 0.3 to 2% and 0.1 to 1%, respectively.

6. The anti-allergic ophthalmic solution according to claim 1, wherein the solution is in a dosage form and the dosage form comprises sterile aqueous eyedrops.

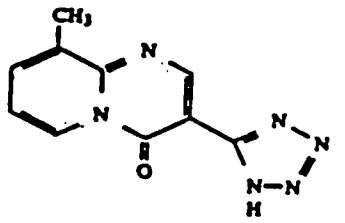
7. An anti-allergic ophthalmic solution prepared by dissolving a potassium salt of the compound of formula (I)



(I)

to provide said salt in a concentration from 0.01 to 1%, in sterile water containing disodium hydrogen phosphate, sodium dihydrogen phosphate and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the disodium hydrogen phosphate and the sodium dihydrogen phosphate are 0.1 to 2% and 0.002 to 1%, respectively.

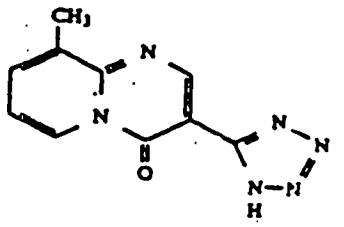
8. An anti-allergic ophthalmic solution prepared by dissolving a potassium salt of the compound of the formula (I)



(I)

to provide said salt in a concentration from 0.01 to 1%, in sterile water containing disodium hydrogen phosphate, potassium dihydrogen phosphate and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the disodium hydrogen phosphate and the potassium dihydrogen phosphate are 0.1 to 1% and 0.002 to 0.7%, respectively.

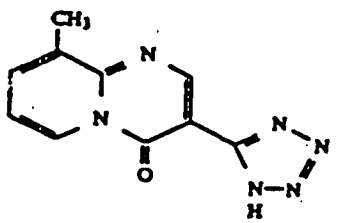
9. An anti-allergic ophthalmic solution prepared by dissolving a potassium salt of the compound of the formula (I),



(I)

to provide salt in a concentration from 0.1 to 1%, in sterile water containing boric acid, sodium borate and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the boric acid and the sodium borate are 0.3 to 2% and 0.3 to 1%, respectively.

10. An anti-allergic ophthalmic solution prepared by dissolving a potassium salt of the compound of the formula (I)



(I)

to provide said salt in a concentration from 0.01 to 1%, in a sterile water containing boric acid, monoethanolamine and optionally one or more pharmaceutically acceptable excipients, wherein the concentrations of the boric acid and the monoethanolamine are 0.3 to 2% and 0.1 to 1%, respectively.

11. A method of treatment of allergic eye diseases which comprises administering to a patient the anti-

allergic ophthalmic solution according to claim 1 in an amount effecti e to treat an allergic eye disease.

12. The method according to claim 11, wherein the solution is topically administered to the eye of the patient in a dosage form and the dosage form comprises sterile aqueous eye drops.

13. A method of treatment of allergic eye diseases which comprises administering to a patient the anti-allergic ophthalmic solution according to claim 2 in an amount effective to treat an allergic eye disease.

14. A method of treatment of allergic eye diseases which comprises administering to a patient the anti-allergic ophthalmic solution according to claim 3 in an amount effective to treat an allergic eye disease.

15. A method of treatment of allergic eye diseases which comprises administering to a patient the anti-allergic ophthalmic solution according to claim 4 in an amount effective to treat an allergic eye disease.

16. A method of treatment of allergic eye diseases which comprises administering to a patient the anti-allergic ophthalmic solution according to claim 5 in an amount effective to treat an allergic eye disease.

17. The anti-allergic ophthalmic solution according to claim 1, wherein the concentration of the potassium salt of the compound of the formula (I) is about 0.1 to 1%.

18. The anti-allergic ophthalmic solution according to claim 2, wherein the concentration of the potassium salt of the compound of the formula (I) is about 0.1 to 1%.

19. The anti-allergic ophthalmic solution according to claim 3, wherein the concentration of the potassium salt of the compound of the formula (I) is about 0.1 to 1%.

20. The anti-allergic ophthalmic solution according to claim 4, wherein the concentration of the potassium salt of the compound of the formula (I) is about 0.1 to 1%.

21. The anti-allergic ophthalmic solution according to claim 5, wherein the concentration of the potassium salt of the compound of the formula (I) is about 0.1 to 1%.

22. A method of treatment of an allergic eye disease which comprises topically administering to a patient the anti-allergic ophthalmic solution according to claim 17 in an amount effective to treat an allergic eye disease.

* * * * *

3/25/99

Santen

SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

Pemirolast Potassium Ophthalmic Solution, 0.1%

(NDA 21-079)

Exclusivity Statement

Exclusivity: Five years of exclusivity is claimed under 314.108 (b) (2).

Pursuant to 21 CFR 314.50 (j) (3) and 314.108 (b) (2), Santen Incorporated certifies that to the best of our knowledge and belief, a drug containing pemirolast potassium has not previously been approved under 505 (b).

Merwin Jerry Hansen
Chief Executive Officer
Santen Incorporated

3/17/99
Date

EXCLUSIVITY SUMMARY for NDA # 21-079 SUPPL # _____

Trade Name ALAMAST Generic Name pemirolast potassium

Applicant Name SANTEN, Inc HFD- 550

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /___/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5yrs

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /✓/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Signature

Title: MEDICAL OFFICER

Raphael Rodriguez 8/6/99
PROJECT MANAGER

_____
Date

/S/

Signature of Division Director
Deputy

8/6/99
Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

NDA 21-079

Santen Incorporated
Attention: Margaret Reents Timms
Vice President Regulatory Affairs and Compliance
555 Gateway Drive
Napa, CA 94558

AUG 23 1999

Dear Ms. Timms:

Reference is made to your correspondence dated April 23, 1999, requesting a waiver of pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Alamast (pemirolast potassium ophthalmic solution) 0.1% for the treatment of allergic conjunctivitis for pediatric populations under three years of age.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact Joanne Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

/S/ 8/23/99

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21079	**Trade Name:**	ALAMAST(PEMIROLAST POTASSIUM OPHTHALMIC)
Supplement Number:		**Generic Name:**	PEMIROLAST POTASSIUM OPHTHALMIC SOL 0.1%
Supplement Type:		**Dosage Form:**	Suspension/Drops; Ophthalmic
Regulatory Action:	AP	**Proposed Indication:**	Allergic Conjunctivitis

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)

____Infants (1-24 Months)

____Children (25 Months-12 years)

____Adolescents (13-16 Years)

_X_ Other Age Groups (listed): age 3 years and above

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Disease does not exist below the age of 3. Studies support all ages above 3. 8/6/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RAPHAEL RODRIGUEZ

/S/

Signature

8-6-99

Date

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND [redacted]

FEB 18 1999

Santen, Inc.
Attention: Michelle A. Carpenter
Director, Regulatory Affairs
555 Gateway Drive
Napa, CA 94558

Dear Ms. Carpenter:

To obtain needed pediatric information on 0.1% Pemirolast Potassium Ophthalmic Solution for the treatment of allergic conjunctivitis, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following two studies:

Studies, Objectives, and Assessments:

1. The first study should be a six-week randomized, double-masked, parallel-group trial of 0.1% Pemirolast Potassium Ophthalmic Solution and placebo (vehicle) applied topically to the eye in at least 30 children, 3 to 5 years of age. The primary objective of the study should be to compare the safety between treatment groups. Safety assessments in addition to the collection of any adverse experiences should include visual acuity and biomicroscopy assessments at approximately weekly intervals. Demographic characteristics, biomicroscopy findings, visual acuity and adverse experiences should be summarized descriptively and compared for each of the two treatment groups.

2. The second study should be a randomized, double-masked, parallel-group trial of approximately 9-16 weeks duration of 0.1% Pemirolast Potassium Ophthalmic Solution and placebo (vehicle) applied topically to the eye in at least 240 patients aged 10 years and older with a history of allergic conjunctivitis. The primary objective of the study should be to compare the ocular clinical response (safety and efficacy) between treatment groups in the treatment of the signs and symptoms associated with allergic conjunctivitis. The primary efficacy variables for this study should be ocular redness and itching. Safety assessments in addition to the collection of any adverse experiences should include visual acuity and biomicroscopy assessments.

Labeling:

Information collected in these studies should permit the determination of appropriate labeling instructions.

Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

At the completion of these studies, full study reports providing the analyses outlined in this request should be provided, with complete analysis, assessment, and interpretation of each study. It is expected that these reports will be submitted at the time of the NDA submission.

Reports of these studies should be submitted with your original new drug application (NDA), with the proposed labeling you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS-PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or mail/messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Raphael Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,

/S/

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Santen

SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

3/25/99

Pemirolast Potassium Ophthalmic Solution, 0.1%

(NDA 21-079)

Debarment Certification

Santen Incorporated certifies that it did not and will not use in any capacity the services of any individual debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug and Cosmetic Act, as amended, 21 U.S. C. §§ 335 (a) and (b), in connection with this application.

Merwin Jerry Hansen
Chief Executive Officer
Santen Incorporated

3/17/99
Date

0100021

Santen

SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

APPEARS THIS WAY
ON ORIGINAL

Pemirolast Potassium Ophthalmic Solution, 0.1%

(NDA 21-079)

GCP Certification

Santen Incorporated hereby certifies that the six clinical studies conducted in the United States under IND [redacted] for the purposes of this New Drug Application were conducted in accordance with Good Clinical Practices and the Declaration of Helsinki. All supporting foreign studies were conducted according to the principles listed in the Declaration of Helsinki.

APPEARS THIS WAY
ON ORIGINAL

Merwin Jerry Hansen
Chief Executive Officer
Santen Incorporated

3/17/99
Date

0100025

Santen

SANTEN INCORPORATED

555 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

20 September 1999

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

RE: NDA #21-079, Pemirolast Potassium Ophthalmic Solution, 0.1%
Response to NDA Deficiencies (Chemistry, Manufacturing, and Controls)
A.019

Dear Dr. Chambers:

This amendment contains Santen's commitment to address all of the Chemistry, Manufacturing, and Controls deficiencies received on September 17, 1999. These commitments are as follows:

The deficiencies received from the Agency are appended to the Form FDA 356h to facilitate review.
If there are any questions regarding this amendment, please contact me at 707-256-2453 or have me paged by calling the general number (707-254-1750). Thank you in advance for your assistance.

Sincerely,

Michelle A. Carpenter

Michelle Carpenter
Director, Regulatory Affairs

Enclosures: Original
1 copy
Raphael Rodriguez, Project Manager (desk copy)

0100001

Santen

SANTEN INCORPORATED
65 Gateway Drive
Napa, California USA 94558
Telephone: 707 254 1750, Facsimile: 707 254 1755

23 September 1999

Wiley Chambers, M.D.
Deputy Division Director
Food and Drug Administration
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Attn: Division Document Room
HFD-550/Rm. N-318
9201 Corporate Blvd.
Rockville, MD 20850-3202

RE: **NDA #21-079, Pemirolast Potassium Ophthalmic Solution, 0.1%**
Final Labeling Text
A.020

Dear Dr. Chambers:

This amendment contains our agreement to the labeling change sent to us by Dr. Boyd today.

To facilitate the process, the revised labeling as sent by the Agency is included in this amendment. Also to facilitate review, the additions/changes have been underlined.

If there are any questions regarding this amendment, please contact me at 707-256-2453 or have me paged by calling the general number (707-254-1750).

Sincerely,

Michelle A Carpenter

Michelle Carpenter
Director, Regulatory Affairs

Enclosures: Original
1 copy
Raphael Rodriguez, Project Manager