CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-048/22-223

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-048
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	May 29, 2007
DRUG NAME:	Triesence™ (triamcinolone acetonide (TA) injectable suspension) 40 mg/ml
INDICATION:	For treatment of the following ophthalmic diseases: [redacted] sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical corticosteroids and [redacted] visualization during vitrectomy
SPONSOR:	Alcon, Inc., Fort Worth, TX 76134
DOCUMENTS REVIEWED:	Vol. 1-5 (Modules 1, 2, & 4)
REVIEW DIVISION:	Division of Anti-Infective and Ophthalmology Products

PHARM/TOX REVIEWER:	Conrad H. Chen, Ph.D.
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Date of review submission to Division File System (DFS): October 23, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
The approval is recommended.

B. Recommendation for nonclinical studies
The ongoing ocular tissue distribution study in rabbits should be submitted as an Amendment as soon as possible.

C. Recommendations on labeling
1. For "Carcinogenesis, Mutagenesis, Impairment of Fertility", "Pregnancy", and "Nursing Mothers" sections of the proposed labeling, the labeling information in NDA 22-048 and NDA 14-901 should be consulted.
2. The following is recommended for "Animal toxicology and/or pharmacology" section of the proposed labeling:

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
Clinical studies have demonstrated that intravitreal triamcinolone acetonide (off label use of Kenalog-40 in ophthalmic medical community) is effective in reducing ocular inflammatory responses and their sequelae. Extensive clinical experience is evident in a review of published literature dating back to the 1960s and demonstrates that triamcinolone acetonide is safe and effective for a variety of ophthalmic indications. Frequently, Kenalog-40 and BSS have been used together by the ophthalmic medical community. The proposed TA intravitreal formulation contains the ingredients similar to that of marketed Kenalog-40 and Alcon's BSS (balanced salt solution) combined together. However, is removed and the in the proposed formulation. The unpreserved balance-salt formulation of TA probably will provide a decreased risk to the patient.
No non-clinical pharmacokinetic studies have been conducted for the TA intravitreal formulation to date. As recommended by the Agency in response to Pre-NDA Briefing Packet, a single ocular tissue distribution study in rabbits

is currently on-going. The sponsor states that the results of this study will be submitted as an Amendment to NDA 22-048. This study report should be submitted as soon as possible.

Non-clinical information compiled from NDA 14-901 (Kenalog®-40 injection), NDA 20-784 (Nasacort® HFA nasal spray) and the published literature showed that triamcinolone acetonide is non-mutagenic and non-carcinogenic. Like other corticosteroids, triamcinolone acetonide is teratogenic when administered to pregnant animals. These findings are listed in the product labelings of Kenalog®-40 and Nasacort® currently in use.

Alcon has conducted single-dose intravitreal toxicity studies in rabbits (up to 6.25 mg/kg) and monkeys (0.8 mg/kg) using triamcinolone acetonide clinical formulation. The results showed that the drug was well tolerated for up to one month with slight decrease in body weight gain and slight corneal thinning.

Triamcinolone acetonide clinical formulation was non-inflammatory when injected intravitreally in rabbits, non-cytotoxic to mouse L-929 cells in an in vitro assay and non-sensitizing in a guinea-pig maximization assay.

The results of the studies summarized herein provided adequate toxicological characterization of the proposed drug product.

B. Pharmacologic activity

Triamcinolone is a glucocorticosteroid agonist and is used for treatment of arthritis, asthma, dermatitis, corticosteroid-responsive skin disease, and immunosuppressive therapy for inflammatory disorders, rhinitis, and stomatitis. The first triamcinolone drug product was approved in 1957. Triamcinolone drug products are available on the market in various dosage forms: tablet, injections, syrup, eye/ear solution, nasal spray, and metered dose inhalers.

Several animal models of posterior segment disease were used in the non-clinical pharmacology studies. Alcon's triamcinolone ophthalmic suspension showed efficacy against mitogen-mediated posterior uveitis, fibroblast-mediated proliferative vitreoretinopathy, ischemia-induced preretinal neovascularization, and VEGF-induced retinal vascular permeability.

C. Nonclinical safety issues relevant to clinical use

As recommended by the Agency in response to Pre-NDA Briefing Packet, a

[redacted]. The sponsor is recommended to submit the study results as soon as possible.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

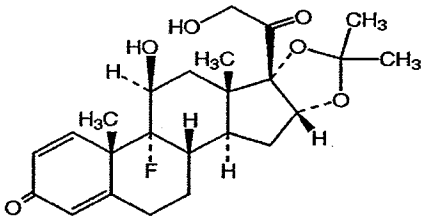
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-048
Review number: No.1
Sequence number/date/type of submission: SN000/May 29, 2007/Original NDA (505 (b)(2)
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Alcon, Inc., Fort Worth, Texas
Manufacturer for drug substance: [redacted]
Reviewer name: Conrad H. Chen, Ph.D.
Division name: Division of Anti-Infective and Ophthalmology Products
Review completion date: September 13, 2007

Drug:

Trade name: Triesence™
Generic name: Triamcinolone Acetonide Injectable Suspension 40 mg/mL
Code name: AL-938 (Alcon), [redacted]
Chemical name: [redacted]

CAS registry number: 76-25-5
Molecular formula/molecular weight: $C_{24}H_{31}FO_6$ /434.50
Structure:



Relevant INDs/NDAs/DMFs: NDA 14-901 (Kenalog®-40 triamcinolone acetonide injectable suspension); NDA 20-784 (Nasacort® triamcinolone acetonide nasal spray); NDA 20742 (Alcon's Balanced Salt Solution, BSS®)

Drug class: Corticosteroid

Indication: For treatment of the following ophthalmic diseases: [redacted] sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical corticosteroids and [redacted] visualization during vitrectomy

Clinical formulation: Suspension for injection (see below)

Table 2.4.1-1

Comparison of Alcon's Triamcinolone Acetonide Injectable Suspension, KENALOG®-40 (NDA 14-901) and Alcon's BSS (NDA 20-742) Product Compositions

Component	Alcon Triamcinolone Acetonide Injection (mg/mL)	KENALOG®-40[a] (mg/mL)	Alcon BSS® (mg/mL)
Triamcinolone Acetonide	40	40	-
Carboxymethylcellulose Sodium	5.0	7.5	-
Polysorbate 80	0.15	0.4	-
Benzyl Alcohol	-	9.9	-
Sodium Chloride		—	6.4
Potassium Chloride		-	0.75
Calcium Chloride (Dihydrate)		-	0.48
Magnesium Chloride (Hexahydrate)		-	0.3
Sodium Acetate (Trihydrate)		-	3.9
Sodium Citrate (Dihydrate)		-	1.7
Sodium Hydroxide and/or Hydrochloric Acid		Adjust to pH 5.0 to 7.5	Adjust to pH — (Target pH 7.5)
Water for Injection			

[a] Information obtained from the KENALOG®-40 package insert; - = not present.

Route of administration: Intravitreal Injection

Proposed use:
Dosage for treatment of ophthalmic conditions: The initial recommended dose is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dosage of 4 mg as needed over the course of treatment.
Dosage for visualization during vitrectomy: The recommended dose is 1 to — µl — of 40 mg/mL suspension) administered intravitreally.

OVERVIEW OF THE SUBMISSION:
This NDA is being submitted pursuant to the provisions of Section 505(b)(2). Except for a few toxicology studies conducted by the sponsor, Alcon intends to cross-reference the approved NDA 14-901 (Kenalog®-40 injection), NDA 20-784 (Nasacort® HFA nasal spray) and the published literature for most of the non-clinical information.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Regulatory History: Triamcinolone is a glucocorticosteroid agonist and is used for treatment of arthritis, asthma, dermatitis, corticosteroid-responsive skin disease, and immunosuppressive therapy for inflammatory disorders, rhinitis, and stomatitis. The first triamcinolone drug product was approved in 1957. Triamcinolone drug products are available on the market in various dosage forms: tablet, injections, syrup, eye/ear solution, nasal spray, and metered dose inhalers.

Several animal models of posterior segment disease were used in the non-clinical pharmacology studies. Alcon's triamcinolone ophthalmic suspension showed efficacy against mitogen-mediated posterior uveitis, fibroblast-mediated proliferative vitreoretinopathy, ischemia-induced preretinal neovascularization, and VEGF-induced retinal vascular permeability.

Clinical studies have demonstrated that intravitreal triamcinolone acetonide (off label use) is effective in reducing ocular inflammatory responses and their sequelae. Extensive clinical experience is evident in a review of published literature dating back to the 1960s and demonstrates that triamcinolone acetonide is safe and effective for a variety of ophthalmic indications.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Table 2.6.3-2

Primary Pharmacology: Mechanism of Action and Efficacy

Test	Species	Dose	Route of Admin.	Method of Assessment	Results	GLP	Location in Module 4
Single Intravitreal Injection	Rabbit	4%; w/v	Intravitreal injection		All formulations remained visible while gradually precipitating to the inferior vitreous cavity. No empirical steroid complications were observed	No	TDOC-0000833 Module 4, Section 4.2.1.1
Posterior Segment Inflammation Induced by Concanavalin-A	Rabbit	4%, 16%, 25%; w/v	Intravitreal injection		All concentrations of TA produced reductions in inflammatory markers equivalent to those produced by dexamethasone (0.5%) and commercial TA.	No	TDOC-0000728 Module 4, Section 4.2.1.1
Proliferative Vitreoretinopathy	Rabbit	2 & 8 mg	Intravitreal injection		2 mg TA significantly reduced retinal detachments vs control eyes by 26% on Day 14 and 34% on Day 28; 8 mg significantly reduced retinal detachments by 26% and 21%. Clinically visible NV was reduced from 74% in control eyes to 33% (2 mg TA) and 8% (8 mg TA).	No	TR 013:3320:0487 Module 4, Section 4.2.1.1

Table 2.6.3-2 (cont.)

Primary Pharmacology: Mechanism of Action and Efficacy

Test	Species	Dose	Route of Admin.	Method of Assessment	Results	GLP	Location in Module 4
Oxygen-induced Retinopathy	Rat	4% and 25%; w/v	Intravitreal injection		4% TA reduced preretinal NV compared to contralateral vehicle treated eyes and untreated controls. 25% TA showed 100% inhibition of NV w/ no significant difference compared to the contralateral eye, indicating a cross-over effect.	No	TDOC-0003417 Module 4, Section 4.2.1.1
VEGF-induced Retinal Vascular Permeability	Rat	4% and 25%; w/v	Intravitreal injection		Retinal vascular permeability was significantly decreased in eyes treated with 0.5% dexamethasone and 4% Alcon TA, compared to vehicle-injected eyes. No statistical difference was seen between 25% Alcon TA or KENALOG®-40 and vehicle-treated eyes; possibly due to a cross-over effect.	No	TDOC-0003413 Module 4, Section 4.2.1.1

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

A considerable body of information has been reported in the literature on the absorption, distribution, metabolism and excretion of triamcinolone acetonide in humans. The pharmacokinetic parameters of systemic administration of TA have been documented in NDA 20-784. A limited number of pharmacokinetic studies of triamcinolone acetonide in animals showed that triamcinolone is cleared from vitreous humor following intravitreal injection in rabbits. (References in the submission: Scholes et al., 1985; Schindler et al., 1982; Kim et al., 2006; Robinson et al., 2006). None of these studies have evaluated the systemic absorption of intravitreally administered triamcinolone acetonide.

As recommended by the Agency in response to Pre-NDA Briefing Packet, a single ocular tissue distribution study in rabbits is currently on-going. The sponsor states that the results of this study will be submitted as an Amendment to NDA 22-048.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No non-clinical pharmacokinetic studies have been conducted for the TA intravitreal formulation to date. A study is currently ongoing to characterize the distribution of TA Injectable Suspension in rabbits. Once completed, this report will be submitted as an Amendment to NDA 22-048.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Non-clinical information compiled from NDA 14-901 (Kenalog®-40 injection), NDA 20-784 (Nasacort® HFA nasal spray) and the published literature showed that triamcinolone acetonide is non-mutagenic and non-carcinogenic. Like other corticosteroids, triamcinolone acetonide is teratogenic when administered to pregnant animals. These findings are listed in the product labelings of Kenalog®-40 and Nasacort® currently in use. Animal studies in which corticosteroids have been given to pregnant mice, rats, rabbits, and monkeys have yielded an increased incidence of cleft palate in the offspring.

Alcon has conducted single-dose intravitreal toxicity studies in rabbits (up to 6.25 mg/kg) and monkeys (0.8 mg/kg) using triamcinolone acetonide clinical formulation. The results showed that the drug was well tolerated for up to one month with slight decrease in body weight gain and slight corneal thinning.

Triamcinolone acetonide clinical formulation was non-inflammatory when injected intravitreally in rabbits, non-cytotoxic to mouse L-929 cells in an in vitro assay and was non-sensitizing in a guinea-pig maximization assay.

2.6.6.2 Single-dose toxicity

Study title: Two-week ocular evaluation of triamcinolone acetonide (TA) suspension following a single intravitreal injection in New Zealand White Rabbits

Key study findings: A single intravitreal injection of TA Injection Suspension showed no adverse ocular effects in rabbits, other than slight body weight and corneal thickness reductions.

Study no.: TDOC-0004294
Volume #, and page #: Vol. 3
Conducting laboratory and location: Alcon Research, Ltd., Fort Worth, Texas 76134
Date of study initiation: March 14, 2006
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: Triamcinolone acetonide (4.0%) 06-43164-2
Methods

Doses: 0, 2, 4, and 10 mg total dose/eye/animal in clinical formulation
Species/strain: New Zealand White Rabbit
Number/sex/group or time point (main study): Seven groups, 3/sex/group
Route, formulation, volume, and infusion rate: A single intravitreal injection to the right eye (OD); the left eye (OS) served as the untreated control.

Table 6.1.3.-1:
Treatment Groups and Treatment Regimen

Group No./ Treatment	No. of Animals		Treatment Volume (mL) per injection	Minimum Study Duration (Observation Days)
	M	F		
1 / Vehicle	3	3	0.10	14
2 / Vehicle	3	3	0.25	14
3 / BSS Sterile Irrigating Solution (Alcon Laboratories, Ft. Worth, TX)	3	3	0.25	14
4 / Triamcinolone Acetonide (4.0%)	3	3	0.05	14
5 / Triamcinolone Acetonide (4.0%)	3	3	0.10	14
6 / Triamcinolone Acetonide (4.0%)	3	3	0.25	14
7 / Kenalog-40 (Bristol-Meyers Squibb Co. Princeton, NJ.)	3	3	0.10	14

Age: Approximately 3 months
Weight (nonrodents only): 2.6-3.4 kg

Observation times and results

No mortalities, pharmacotoxic signs on general health were observed throughout the study. Body weights for the 0.25 mL TA group (Group 6) were significantly less than those in the 0.1 mL vehicle control group at Study Day 8, and body weights for the 0.1 mL and 0.25 mL TA groups (Groups 5 and 6), as well as the 0.1 mL Kenalog-40 group (Group 7), were significantly less than those in the 0.1 mL vehicle control group at Day 14. Because of the small changes, the changes in body weight, although statistically significant, probably are not toxicologically meaningful.

Biomicroscopic slit-lamp examinations, intraocular pressure measurements, specular microscopic examinations, indirect ophthalmoscopic examinations and histopathologic examinations did not show any significant treatment-related effects on the eyes of animals.

Treatment related decreases in corneal thickness were observed. Corneal thickness in the right eyes of the 0.05 mL TA group were significantly less than those of the 0.10 mL vehicle control group at Study Days 4, 7 and 14. Similarly, the right eyes of the 0.25 mL TA group demonstrated significantly decreased corneal thickness than 0.1 mL vehicle control group on Study Days 7 and 14. The Study Day 14 corneal thickness mean for the Kenalog-40 group was also significantly less than that of 0.1 mL vehicle control group. The sponsor stated that the reduced corneal thickness in TA groups in this study is consistent with observations made in the sponsor's laboratory when topical ocular corticosteroids were administered to rabbits (International Journal of Toxicity (24): 419-425).

The changes of body weight and corneal thickness were shown in the following tables:

Table 1 Body Weights (kg)

Body Weights (kg)		Group						
		0.1 mL Vehicle	0.25 mL Vehicle	BSS Sterile Irrigating Solution	0.05 mL Triamcinolone Acetonide (4.0%)	0.1 mL Triamcinolone Acetonide (4.0%)	0.25 mL Triamcinolone Acetonide (4.0%)	Kenalog-40
Period								
Pre-Screen	Mean	2.767	2.783	2.883	2.817	2.767	2.700	2.700
	Std [a]	0.08	0.13	0.28	0.08	0.08	0.06	0.06
	N	6	6	6	6	6	6	6
Day 8	Mean	2.883	2.900	2.917	2.800	2.750	*2.700	2.733
	Std [a]	0.12	0.09	0.10	0.11	0.08	0.11	0.12
	N	6	6	6	6	6	6	6
Day 14	Mean	2.900	2.933	2.917	2.767	*2.717	*2.617	*2.633
	Std [a]	0.09	0.05	0.10	0.10	0.10	0.12	0.08
	N	6	6	6	6	6	6	6

[a] Std = Standard Deviation
* Indicates the following group mean is significantly different ($p \leq 0.05$) from the 0.1 mL Vehicle mean. Based on results from Dunnett's test.

Table 2 Pachymetry (µm) for OD

Pachymetry (µm) OD		Group						
		0.1 mL Vehicle	0.25 mL Vehicle	BSS Sterile Irrigating Solution	0.05 mL Triamcinolone Acetonide (4.0%)	0.1 mL Triamcinolone Acetonide (4.0%)	0.25 mL Triamcinolone Acetonide (4.0%)	Kenalog-40
Period								
Pre-Screen	Mean	366.833	359.887	354.668	355.222	368.000	367.777	362.890
	Std [a]	11.87	18.86	8.53	8.35	8.10	19.54	22.81
	N	6	6	6	6	6	6	6
Day 2	Mean	345.445	358.723	345.222	328.945	341.390	341.500	334.335
	Std [a]	21.14	17.05	7.33	17.82	11.98	14.22	19.76
	N	6	6	6	6	6	6	6
Day 4	Mean	370.665	378.000	375.055	*333.777	347.387	341.112	344.277
	Std [a]	24.31	24.03	11.35	15.36	13.60	22.70	18.32
	N	6	6	6	6	6	6	6
Day 7	Mean	370.278	378.165	366.277	*333.777	342.333	*338.833	340.110
	Std [a]	12.06	27.04	7.66	18.56	19.96	16.50	27.72
	N	6	6	6	6	6	6	6
Day 14	Mean	370.720	379.555	369.557	*328.777	346.055	*339.168	*335.555
	Std [a]	23.29	24.16	1.15	20.91	14.64	16.64	18.34
	N	6	6	6	6	6	6	6

[a] Std = Standard Deviation
* Indicates the following group mean is significantly different ($p \leq 0.05$) from the 0.1 mL Vehicle mean. Based on results from Dunnett's test.

Study title: Evaluation of triamcinolone acetonide (TA) PVP following intravitreal injection in New Zealand White Rabbits

Key study findings: Intravitreal administration of TA at single dose of up to 25 mg, in a volume of 0.1 mL in rabbits, resulted in no significant adverse effects or ocular toxicity. However, basophilic drug material was present in the vitreous body throughout the observation period.
Study no.: TDOC-0002414
Volume #, and page #: Vol. 4
Conducting laboratory and location: Alcon Research Ltd.

Date of study initiation: May 20, 2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: 03-33786 (- %), 03-33787 (-,%), and 03-33788 (— %)
Methods

Doses: BSS, formulation vehicle control, 4 mg (4% suspension), 16 mg (16% suspension), and 25 mg (25% suspension)
Species/strain: New Zealand White Rabbits
Number/sex/group or time point (main study): 4/sex/group (total 5 groups)
Route, formulation, volume, and infusion rate: a single intravitreal injection (0.1 mL) to the right eye (OD); the left eye was an untreated control; all animals were observed for 35 days post-dose
Age: 7-8 months
Weight (nonrodents only): 3.7-4.6 kg
Unique study design or methodology (if any):

Observation times and results

No mortalities or significant pharmacotoxic signs on general health were observed in any animals. No statistically significant differences in mean body weights were found between the control and treatment groups. Following the intravitreal injection, the opaque white test article was clearly visible in the vitreous body for all TA treated groups, and remained so throughout the observation period. The incidence of this finding was 6/8, 8/8 and 8/8 for the 4, 16 and 25 mg TA groups, respectively. No other significant adverse ocular effects were observed in any groups.
Corneal thickness was statistically significantly reduced only for males of the 4 and 16 mg groups. No pathological changes were observed in the retina or other ocular structures.

Study title: Intravitreal inflammatory test in New Zealand White Rabbits with triamcinolone acetonide (TA)

Key study findings: Under the conditions of this test, Triamcinolone Acetonide (4%) Sterile Suspension in balanced salt solution containing 0.015% polysorbate-80 showed no evidence of causing inflammation in NZW rabbits.
Study no.: TDOC-0003842
Volume #, and page #: Vol. 5
Conducting laboratory and location: ————————————
Date of study initiation: September 14, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: 05-40789-1
Methods

Doses: 0.2 mL of 4% (40 mg/mL) TA in 0.015% Polysorbate-80 in balanced salt solution (clinical formulation) was injected into the right eye of six rabbits
Species/strain: New Zealand White Rabbits
Number/sex/group or time point (main study): 6 rabbits total

Route, formulation, volume, and infusion rate: Single intravitreal injection with 0.2 mL test solution into the right eye (OD) and with 0.2 mL balanced salt solution into the left eye (OS)
Age: 4-5 months
Weight (nonrodents only): 4.1-4.5 kg

Observation times and results

Eyes were observed at the end of day and on Study Days 1 and 2 for gross irritation. No significant changes were noted in the ocular tissues examined by slit-lamp and ophthalmoscope. After the terminal biomicroscopic evaluation on Study Day 2, rabbits were euthanatized and white blood cell (WBC) counts were performed on samples of vitreous from the treated and control eyes. Mean WBC counts in the vitreous fluid were 7.5 cells/mm^3 for the test (OD) eyes and 5.8 cells/mm^3 for the control (OS) eyes. Counts less than 200 cells/mm^3 were considered to be acceptable. It was concluded that TA (40 mg/mL) Sterile Suspension in balanced salt solution containing 0.015% polysorbate-80 showed no evidence of causing inflammation in rabbits.

Study title: Intraocular irritation of triamcinolone acetonide (TA) and AL02178 (anti-inflammatory corticosteroids) in primates

Key study findings: The intraocular administration of 2 mg TA or AL02178 in primates produced only minimal, transient ocular effects that were due to the normal sequela of recovery from an invasive procedure represented by both the intraocular injection and the vitrectomy procedure. No drug-related effects were observed in general health or ophthalmic parameters.
Study no.: TR 043:3320:0887
Volume #, and page #: Vol. 4
Conducting laboratory and location: Alcon Research, Ltd.
Date of study initiation: March 25, 1987
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity:
Methods

Doses: 2 mg of TA or AL02178 in 0.1 mL; the vehicle contains 1% polyethylene glycol/0.005% tyloxapol in BSS (not the clinical formulation)

Table 2

Treatment Groups and Treatment Regimen Used in the Intraocular Irritation Evaluation of Triamcinolone Acetonide and AL02178 in Primates

Group		Test Article	Primates (M)	(F)		Treatment	Obs. Days
1		Vehicle	1	1	(2)	Partial Vitrectomy	33
2		Vehicle	1	1	(2)	No Vitrectomy	33
3	2 mg	Triamcinolone Acetonide	2	2	(4)	Partial Vitrectomy	33
4	2 mg	Triamcinolone Acetonide	2	2	(4)	No Vitrectomy	33
5	2 mg	AL02178	2	2	(4)	Partial Vitrectomy	33
6	2 mg	AL02178	2	2	(4)	No Vitrectomy	33

Species/strain: Cynomolgus monkeys (Macaca fascicularis)
Number/sex/group or time point (main study): 2/sex/group
Route, formulation, volume, and infusion rate: Single intravitreal injection into the right eye with and without vitrectomy; the left eye served as an untreated control; followed by a one month observation period.
Age: No information is available
Weight (nonrodents only): 2.0-3.2 kg

Observation times and results

No drug-related effects were observed in general health or ophthalmic parameters, though ocular findings related to the partial vitrectomy procedure (e.g. transient conjunctival congestion, swellings and discharge, impaired papillary light reflex, flare and corneal cloudiness) were evident. The observed ocular changes were considered to be due to the normal sequela of recovery from an invasive procedure represented by both the intraocular injection and the vitrectomy procedure.

It was concluded that the intraocular administration of 2 mg TA or AL02178 produced only minimal, transient ocular effects that were procedural (injection or vitrectomy) in nature.

2.6.6.3 Repeat-dose toxicity

No non-clinical repeat-dose toxicity study for Triamcinolone Acetonide Injectable Suspension 40 mg/mL was conducted. The package insert for Kenalog®-40 notes that prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

2.6.6.4 Genetic toxicology

Information is available in NDA 20-784 (Nasacort® triamcinolone acetonide nasal spray). No evidence of mutagenicity was detected from *in vitro* tests (a reverse mutation

test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells) conducted with triamcinolone acetonide.

2.6.6.5 Carcinogenicity

Information is available in NDA 20-784 (Nasacort® triamcinolone acetonide nasal spray).

In a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 1.0 mcg/kg (approximately 1/30 and 1/50 of the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively). In a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 3.0 mcg/kg (approximately 1/12 and 1/30 of the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively).

2.6.6.6 Reproductive and developmental toxicology

Information is available in NDA 14-901 (Kenalog®-40 triamcinolone acetonide injectable suspension) and NDA 20-784 (Nasacort® triamcinolone acetonide nasal spray).

Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring.

Pregnancy Category C. Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. In rats, triamcinolone acetonide was teratogenic at inhalation doses of 20 mcg/kg and above (approximately 7/10 of the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). In rabbits, triamcinolone acetonide was teratogenic in inhalation doses of 20 mcg/kg and above (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). In monkeys, triamcinolone acetonide was teratogenic in inhalation dose of 500 mcg/kg (approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in the monkey were cranial malformations.

2.6.6.7 Local tolerance

Refer to 2.6.6.2 Single-dose toxicity study for information.

2.6.6.8 Special toxicology studies

Study title: Agarose overlay assay in the L-929 mouse fibroblast cell line with triamcinolone acetonide (TA)

Key study findings: Under the condition of the study, the TA formulation was considered non-cytotoxic and meets the requirements of the ISO10993-5 agar diffusion test.

Study no.: TDOC-0003840

Volume #, and page #: Vol. 3

Conducting laboratory and location: [redacted]

Date of study initiation: September 21, 2005
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: 05-40789-1
Formulation/vehicle: TA (4.0%) containing polysorbate-80 (0.015%) in BSS
Methods and Results:
A cytotoxicity assay was conducted to determine the biological reactivity of L-929 mouse fibroblast cells in response to 4% TA in balanced salt solution (BSS) containing 0.015% polysorbate-80 (TA Suspension). This study was conducted based on the EN ISO 10993-5 guideline (Biological Evaluation of Medical Devices-Part 5: Tests for *In Vitro* Cytotoxicity). Slight biological reactivity (Grade 1) was observed in the L929 mammalian cells at 48 hours, post exposure to the test article. The observed cellular response obtained from the positive control article (Grade 3) and negative control (Grade 0) confirmed the suitability of the test system.
Under the condition of the study, the TA formulation was considered non-cytotoxic and meets the requirements of the ISO10993-5 agar diffusion test.

Study title: Guinea pig maximization assay with triamcinolone acetonide (TA)

Key study findings: TA (4%) in polysorbate-80 (0.015%) elicited no reaction at the challenge (0% sensitization), following an induction phase. This is a Grade 1 reaction (scoring system of Kligman) and the test article is classified as having weak allergenic potential.
Study no.: TDOC-0003841
Volume #, and page #: Vol. 5
Conducting laboratory and location: [redacted]
Date of study initiation: June 14, 2005
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: 05-40789-1
Formulation/vehicle: Triamcinolone Acetonide (4%) Sterile Suspension in balanced salt solution containing polysorbate-80 (0.015%)
Methods:
A maximization assay was conducted with 4% Triamcinolone Acetonide (TA) in balanced salt solution (BSS) containing 0.015% polysorbate-80 (TA Suspension) to evaluate the potential for delayed dermal contact sensitization. This non-clinical study was based on the EN ISO 10993-10 guideline (Biological Evaluation of Medical Devices-Part 10: Tests for Irritation and Delayed-Type Hypersensitivity).
Results:
Based on the standards set by the study protocol, the test article, TA (4%) in polysorbate-80 (0.015%) elicited no reaction at the challenge (0% sensitization), following an induction phase. Therefore, as defined by the scoring system of Kligman, this is a Grade 1 reaction (Allergic Contact Dermatitis I the Guinea Pig. Identification of Contact Allergens. Springfield, IL.: Thomas, 1970) and the test article is classified as having weak allergenic potential.

2.6.6.9 Discussion and Conclusions

Non-clinical information compiled from NDA 14-901 (Kenalog®-40 injection), NDA 20-784 (Nasacort® HFA nasal spray) and the published literature showed that triamcinolone acetonide is non-mutagenic and non-carcinogenic. Like other corticosteroids, triamcinolone acetonide is teratogenic when administered to pregnant animals. These findings are listed in the product labelings of Kenalog®-40 and Nasacort® currently in use. Animal studies in which corticosteroids have been given to pregnant mice, rats, rabbits, and monkeys have yielded an increased incidence of cleft palate in the offspring.

Alcon has conducted single-dose intravitreal toxicity studies in rabbits (up to 6.25 mg/kg) and monkeys (0.8 mg/kg) using triamcinolone acetonide clinical formulation. The results showed that the drug was well tolerated for up to one month with slight decrease in body weight gain and slight corneal thinning.

Triamcinolone acetonide clinical formulation was non-inflammatory when injected intravitreally in rabbits, non-cytotoxic to mouse L-929 cells in an *in vitro* assay and non-sensitizing in a guinea-pig maximization assay.

The results of the non-clinical studies summarized herein provided adequate toxicological characterization of the proposed drug product.

2.6.6.10 Tables and Figures

The relevant tables have been listed under individual sections.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Table: 2.6.7-1

Toxicology Overview

Test Article: Triamcinolone Acetonide Injectable Suspension

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses	GLP	Testing Facility	Study Number	Location
Local Tolerance	NZW Rabbit	Intravitreal Injection	Single Dose	0, 2, 4, and 10 mg total dose	Yes	Alcon	TDOC-0004294	Module 4, Section 4.2.3.6
	NZW Rabbit	Intravitreal Injection	Single Dose	0, 4, 16 and 25 mg total dose	Yes	Alcon	TDOC-0002414	Module 4, Section 4.2.3.6
	NZW Rabbit	Intravitreal Injection	Single Dose	8 mg total dose	Yes	NAmSA	TDOC-0003842	Module 4, Section 4.2.3.6
	Cynomolgus Monkey	Intravitreal injection with and without vitrectomy	Single Dose	2 mg total dose	Yes	Alcon	043:3320:0887	Module 4, Section 4.2.3.6
Other Toxicity Studies	Guinea Pig	Maximization Assay	72 Hours following Challenge	40 mg/ml	Yes	—	TDOC-0003841	Module 4, Section 4.2.3.7.1
	L-929 Mouse Fibroblast Cells	Agarose Overlay	Single Dose	40 mg/ml	Yes	—	TDOC-0003840	Module 4, Section 4.2.3.3.1

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Triamcinolone is a glucocorticosteroid agonist and is used for treatment of arthritis, asthma, dermatitis, corticosteroid-responsive skin disease, and immunosuppressive therapy for inflammatory disorders, rhinitis, and stomatitis. The first triamcinolone drug product was approved in 1957. Triamcinolone drug products are available on the market in various dosage forms: tablet, injections, syrup, eye/ear solution, nasal spray, and metered dose inhalers.

Clinical studies have demonstrated that intravitreal triamcinolone acetonide (off label use of Kenalog-40) is effective in reducing ocular inflammatory responses and their sequelae. Extensive clinical experience is evident in a review of published literature dating back to the 1960s and demonstrates that triamcinolone acetonide is safe and effective for a variety of ophthalmic indications. Frequently, Kenalog-40 and BSS have been used together by the ophthalmic medical community. The proposed TA intravitreal formulation contains the ingredients similar to that of marketed Kenalog-40 and Alcon's BSS (balanced salt solution) added together. However, benzyl alcohol is removed and the amounts of polysorbate-80 and caboxymethylcellulose (CMC) are reduced in the proposed formulation.

No non-clinical pharmacokinetic studies have been conducted for the TA intravitreal formulation to date. As recommended by the Agency in response to Pre-NDA Briefing Packet, a single ocular tissue distribution study in rabbits is currently on-going. The sponsor states that the results of this study will be submitted as an Amendment to NDA 22-048.

Non-clinical information compiled from NDA 14-901 (Kenalog®-40 injection), NDA 20-784 (Nasacort® HFA nasal spray) and the published literature showed that triamcinolone acetonide is non-mutagenic and non-carcinogenic. No evidence of mutagenicity was detected from *in vitro* tests (a reverse mutation test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells) conducted with triamcinolone acetonide. In a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 1.0 mcg/kg (approximately 1/30 and 1/50 of the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively). In a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 3.0 mcg/kg (approximately 1/12 and 1/30 of the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively).

Like other corticosteroids, triamcinolone acetonide is teratogenic when administered to pregnant animals. These findings are listed in the product labelings of Kenalog®-40 and Nasacort® currently in use. Animal studies in which corticosteroids have been given to pregnant mice, rats, rabbits, and monkeys have yielded an increased incidence of cleft palate in the offspring.

Alcon has conducted single-dose intravitreal toxicity studies in rabbits (up to 6.25 mg/kg) and monkeys (0.8 mg/kg) using triamcinolone acetonide clinical formulation. The results showed that the drug was well tolerated for up to one month with slight decrease in body weight gain and slight corneal thinning.

Triamcinolone acetonide clinical formulation was non-inflammatory when injected intravitreally in rabbits, non-cytotoxic to mouse L-929 cells in an in vitro assay and non-sensitizing in a guinea-pig maximization assay.
The results of the studies summarized herein provided adequate toxicological characterization of the proposed drug product.

Unresolved toxicology issues (if any): None.

Recommendations:
The approval of NDA 22-048 is recommended.

Suggested labeling:
See the recommendations in Executive Summary.

Signatures (optional):

Reviewer Signature ___Conrad H. Chen, Ph.D.,
Pharmacologist_____

Supervisor Signature____Wendelyn Schmidt, Ph.D., Acting Pharmacology Team Leader_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

None

Appears This Way
On Original

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

/s/

Conrad Chen
10/23/2007 02:09:35 PM
PHARMACOLOGIST
The approval of NDA 22-048 is recommended.

Wendelyn Schmidt
10/25/2007 04:03:49 PM
PHARMACOLOGIST

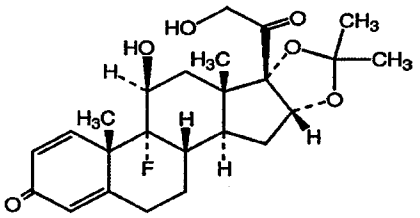
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22-048
Review number: No. 2
Sequence number/date/type of submission: SN000BP/September 25, 2007/Original NDA (BP)
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Alcon, Inc., Fort Worth, Texas
Manufacturer for drug substance: [redacted]
Reviewer name: Conrad H. Chen, Ph.D.
Division name: Division of Anti-Infective and Ophthalmology Products
Review completion date: October 31, 2007

Drug:

Trade name: Triesence™
Generic name: Triamcinolone Acetonide Injectable Suspension 40 mg/mL
Code name: AL-938 (Alcon), [redacted]
Chemical name: [redacted]

CAS registry number: 76-25-5
Molecular formula/molecular weight: $C_{24}H_{31}FO_6$ /434.50
Structure:



Relevant INDs/NDAs/DMFs: NDA 14-901 (Kenalog®-40 triamcinolone acetonide injectable suspension); NDA 20-784 (Nasacort® triamcinolone acetonide nasal spray); NDA 20742 (Alcon's Balanced Salt Solution, BSS®)

Drug class: Corticosteroid

Indication: For treatment of the following ophthalmic diseases: [redacted] sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical corticosteroids, [redacted] visualization during vitrectomy

Clinical formulation: Suspension for injection (see below)

Table 2.4.1-1

Comparison of Alcon's Triamcinolone Acetonide Injectable Suspension, KENALOG®-40 (NDA 14-901) and Alcon's BSS (NDA 20-742) Product Compositions

Component	Alcon Triamcinolone Acetonide Injection (mg/mL)	KENALOG®-40[a] (mg/mL)	Alcon BSS® (mg/mL)
Triamcinolone Acetonide	40	40	-
Carboxymethylcellulose Sodium	5.0	7.5	-
Polysorbate 80	0.15	0.4	-
Benzyl Alcohol	-	9.9	-
Sodium Chloride			6.4
Potassium Chloride		-	0.75
Calcium Chloride (Dihydrate)		-	0.48
Magnesium Chloride (Hexahydrate)		-	0.3
Sodium Acetate (Trihydrate)		-	3.9
Sodium Citrate (Dihydrate)		-	1.7
Sodium Hydroxide and/or Hydrochloric Acid		Adjust to pH 5.0 to 7.5	Adjust to pH (Target pH 7.5)
Water for Injection			

[a] Information obtained from the KENALOG®-40 package insert; - = not present.

Route of administration: Intravitreal Injection

Proposed use:
Dosage for treatment of ophthalmic conditions: The initial recommended dose is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dosage of 4 mg as needed over the course of treatment.
Dosage for visualization during vitrectomy: The recommended dose is 1 to of 40 mg/mL suspension) administered intravitreally.

Non-clinical study reviewed in this submission:

Pharmacokinetic study:
Study title: Ocular distribution of radioactivity following intravitreal injection of ^{14}C-AL-938 (Triamcinolone Acetonide Ophthalmic Suspension) to male New Zealand White rabbits

Key study findings: Following a 2.1 mg intravitreal dose of ^{14}C-AL-938 to the rabbit eye, highest concentrations of radioactivity were in the retina and choroid. In the aqueous humor, iris-ciliary body and lens, the radioactivity levels were at least 7-fold lower than

in the retina. The intravitreal dose resulted in very low systemic drug levels as evidenced by plasma concentrations that were more than 10,000-fold lower than that in retina and not quantifiable (5 ng eq/g) after 4 hours.

Study no.: TDOC-0005863
Volume #, and page #: C 7.1, Page 1
Conducting laboratory and location: Alcon Research, Ltd., Fort Worth, Texas
Date of study initiation: June 11, 2007
GLP compliance: not stated
QA report: yes (x) no ( )
Drug, lot #, and % purity: not stated

Methods

Doses: a single intravitreal injection of 2.1 mg triamcinolone acetonide (50 µl of a 40.4 mg/g ^{14}C-AL-938 ophthalmic suspension) to the right (OD) eye
Species/strain: male New Zealand white rabbits
Number/sex/group or time point (main study): 61 animals, 4 animals per sampling time point
Route, formulation, volume, and infusion rate: intravitreal injection
Weight (nonrodents only): 1.5-3.0 kg

Observation times and results

The pharmacokinetics and ocular tissue distribution of radioactivity were determined following an intravitreal injection of 2.1 mg triamcinolone acetonide (50 µl of a 40.4 mg/g ^{14}C-AL-938 ophthalmic suspension) administered as single unilateral dose to male New Zealand white rabbits. Following administration of test article, ocular tissues and blood were collected at 0.5, 1, 2, 4, 8, 24 and 72 hours and 7, 14, 30, 45, 60 and 88 days. Samples were analyzed for total radioactivity by liquid scintillation counting (LSC) and concentrations of radioactivity were reported as µg equivalents of ^{14}C-AL-938 (µg eq/g).

The intravitreal injection resulted in a centrally located dose depot in the vitreous humor. Dose material was visible in all animals (4/4) through Day 60. At Day 88, no dose material was observed in three of four animals. Radioactive drug equivalents distributed widely throughout the eye. The results (tissue concentrations and $T_{1/2}$) from aqueous humor, conjunctiva, cornea, lens, iris-ciliary body and vitreous humor are shown in the following tables:

Table: 2.6.5.5
Pharmacokinetics: Organ Distribution

Test Article: triamcinolone acetonide
Location in CTD: Vol. Page
Study No. TDOC-0005863

Species: Rabbit, New Zealand White
Gender (M/F) / Number of animals: 4M/time point
Feeding condition: Fasted
Vehicle/Formulation: 4.04% ^{14}C-AL-938 Intravitreal Ophthalmic Suspension
Method of Administration: Intravitreal Injection
Dose: 0.0519 ± 0.0059 g of formulation (2.1 mg triamcinolone acetonide)
Radionuclide: ^{14}C
Specific Activity: 5.788E4 dpm/ug (2.607E1 uCi/mg) of formulation

Time (h)	Mean Concentration (ug/g)					
	Aqueous Humor	Conjunctiva	Cornea	Lens	Iris- Ciliary Body	Vitreous Humor
0.5	0.0091 ± 0.0106	5.88 ± 6.97	3.72 ± 2.66	99.4 ± 136	16 ± 12.1	71.8 ± 30.8
1	0.0516 ± 0.0242	0.526 ± 0.396	2.29 ± 2.47	0.746 ± 0.223*	16.9 ± 22.9	85.6 ± 21.8
2	0.139 ± 0.127	0.834 ± 0.788	1.08 ± 1.09	2.24 ± 1.8	5.71 ± 2.75	96.9 ± 19.6
4	0.291 ± 0.0893	1.39 ± 0.776	3.58 ± 3.56	119 ± 117	16.5 ± 7.9	56.5 ± 39.7
8	0.31 ± 0.033	1.2 ± 0.949	0.575 ± 0.207	1.9 ± 0.578	4.69 ± 2.44	62.9 ± 41.6
24	0.194 ± 0.0174	0.725 ± 0.392	0.495 ± 0.172*	4.95 ± 4.82*	2.76 ± 1.34*	77.4 ± 22
72	0.0403 ± 0.00828	0.483 ± 0.258*	0.164 ± 0.0525	2.3 ± 1.21	6.83 ± 6.2	55.3 ± 12.5
168	0.0201 ± 0.0104	0.0325 ± 0.0235	0.076 ± 0.0196*	1.99 ± 0.774*	0.806 ± 0.742*	87.8 ± 42.1
336	0.00947 ± 0.00166	0.0211 ± 0.0244	0.0639 ± 0.0126	1.5 ± 0.407	0.536 ± 0.138	32.3 ± 30.5
720	0.0086 ± 0.000472*	0.01 ± 0.02	0.0455 ± 0.00396*	1.46 ± 0.496*	0.75 ± 0.646	48.8 ± 39.9
1080	0.00696 ± 0.000987	0.019 ± 0.0144	0.0377 ± 0.00691	0.605 ± 0.124	0.206 ± 0.0403*	19.6 ± 5.21*
1440	0.00478 ± 0.000709*	BLQ	0.0339 ± 0.00689*	0.517 ± 0.141*	0.564 ± 0.469*	98.8 ± 23.9
2112	BLQ	BLQ	0.0209 ± 0.00147*	0.292 ± 0.0638*	0.109 ± 0.00721*	0.0925 ± 0.0938*
$T_{½}$ (days)	31	43	46	29	33	11

Additional Information: * N = 3
BLQ: Below limit of quantitation

Table: 2.6.5.5
Pharmacokinetics: Organ Distribution

Test Article: triamcinolone acetonide
Location in CTD: Vol. Page
Study No. TDOC-0005863

Species: Rabbit, New Zealand White
Gender (M/F) / Number of animals: 4M/time point
Feeding condition: Fasted
Vehicle/Formulation: 4.04% ^{14}C-AL-938 Intravitreal Ophthalmic Suspension
Method of Administration: Intravitreal Injection
Dose: 0.0519 ± 0.0059 g of formulation (2.1 mg triamcinolone acetonide)
Radionuclide: ^{14}C
Specific Activity: 5.788E4 dpm/ug (2.607E1 uCi/mg) of formulation

Time (h)	Mean Concentration (ug/g)					
	Anterior Retina	Posterior Retina	Anterior Choroid	Posterior Choroid	Optic Nerve Head	Plasma
0.5	49.8 ±17.2	61.4 ± 28.8	19.3 ± 4.63*	16 ± 4.94	23.6 ± 15.3*	0 ± 0
1	62.1 ± 62.8	181 ± 185	65.9 ± 57.5	19.4 ± 5.73*	21.6 ± 26.4	0.00945 ± 0.000943
2	65.6 ± 67.4	197 ± 270	20.1 ± 13.7	19.9 ± 12.8	13.2 ± 9.83	0.0121 ± 0.00189
4	73.5 ± 51.2	95 ± 52.2*	29.3 ± 12.8	28 ± 25.6	9.59 ± 3.7	0.0108 ± 0
8	48.3 ± 47.2	61.6 ± 61.7	11.4 ± 5.5	18.7 ± 18.8	17.5 ± 18.2	BLQ
24	18.8 ± 15.2*	22.6 ± 4.37*	34 ± 31.4	8.02 ± 1.87	3.01 ± 0.162*	BLQ
72	167 ± 149*	91.6 ± 91.2	199 ± 274	21.4 ± 11.2	3.71 ± 1.23*	BLQ
168	14 ± 11.3	15.9 ± 11.7	5.51 ± 4.43	7.06 ± 7.71	1.33 ± 1.27	BLQ
336	6.93 ± 7.68	3.27 ± 1.77*	1.49 ± 1.13	1.4 ± 0.586*	0.137 ± 0.0453	BLQ
720	5.1 ± 4.05*	11.5 ± 8.32*	0.808 ± 0.548*	2.5 ± 1.51*	0.662 ± 0.496	BLQ
1080	1.53 ± 0.893*	1.19 ± 0.799*	0.531 ± 0.0687*	0.539 ± 0.442*	0.54 ± 0.814	BLQ
1440	24.6 ± 21.1	12.8 ± 11.1	3.62 ± 2.56	0.837 ± 0.486	2.26 ± 0.441*	BLQ
2112	0.164 ± 0.0661*	0.251 ± 0.0757*	0.547 ± 0.892	BLQ	0.933 ± 0.314	BLQ
$T_{½}$ (days)	18	19	44	19	NC	NC

Additional Information: * N = 3
BLQ: Below limit of quantitation
NC: Not calculable, undefined or insufficient data in terminal elimination phase

The retina (both anterior and posterior) was the tissue with the highest levels of radioactivity (C_{max} and AUC) followed by the choroid (both anterior and posterior). Radioactivity levels in the retina and choroids declined rapidly in the first 7 days; and then declined much more slowly with half lives of approximately 20 days. Radioactivity levels in all other ocular tissues showed a similar initial rapid decline followed by a slower elimination phase. The radioactivity in other ocular tissues was at least 7-fold lower than was observed in retina. Plasma radioactivity levels were very low, and only quantifiable (>5 ng eq/g) for the first four hours after dosing. The results are shown in the following table:

Table 4.3.-1: Mean Pharmacokinetic Parameters of Radioactivity Following a Single Intravitreal Administration of ^{14}C-AL-938 to Male New Zealand White Rabbits

Tissue	C_{max} (ug eq/g)	T_{max} (h)	$T_{½}$ (days)	t_{last} (h)	$AUC_{0\text{-}tlast}$ (ug eq*h/g)	$AUC_{0\text{-}inf}$ (ug eq*h/g)
Aqueous Humor	0.31 ± 0.033	8	31	1440	25.2 ± 0.888	30.4
Conjunctiva	5.88 ± 6.97	0.5	43	1080	96 ± 14.5	124
Cornea	3.72 ± 2.66	0.5	46	2112	132 ± 7.56	165
Lens[a]	4.95 ± 4.82	24	29	2112	2160 ± 174	2450
Iris Ciliary Body	16.9 ± 22.9	1	33	2112	1640 ± 297	1770
Anterior Retina	167 ± 149	72	18	2112	32400 ± 8410	32600
Posterior Retina	197 ± 270	2	19	2112	23000 ± 4800	23200
Anterior Choroid[b]	65.9 ± 57.5	1	44	2112	6820 ± 1480	7660
Posterior Choroid	28 ± 25.6	4	19	2112	4710 ± 747	5280
Optic Nerve Head	23.6 ± 15.3	0.5	NC	4	2750 ± 261	NC
Plasma	0.0121 ± 0.00189	4	NC	1440	0.0361 ± 0.00146	NC

NC: not calculable, undefined or insufficient data in terminal elimination phase

[a] If 0.5 and 4h time points are retained, C_{max} = 119 ± 117 ug eq/g at 4h; $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ equal 2560 ± 249 and 2850 ug eq*h/g, respectively.

[b] If 72h time point is retained, C_{max} = 199 ± 274 ug eq/g at 72h; $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}inf}$ equal 19400 ± 9910 and 20200 ug eq*h/g, respectively.

Conclusion:

The pharmacokinetics and ocular tissue distribution of radioactivity were determined following an intravitreal injection of 2.1 mg triamcinolone acetonide (50 µl of a 40.4 mg/g ^{14}C-AL-938 ophthalmic suspension) administered as single unilateral dose to male New Zealand white rabbits.

The results showed that the highest concentrations of radioactivity were in the retina and choroid. In the aqueous humor, iris-ciliary body and lens, the radioactivity levels were at least 7-fold lower than in the retina. The intravitreal dose resulted in very low systemic drug levels (approximately 10 ng eq./g at 1, 2, and 4 hours) and plasma concentrations that were more than 10,000-fold lower than that in retina and not quantifiable (<5 ng eq/g) after 4 hours.

Recommendation:

In the Memorandum to the file for PIND —— dated September 5, 2006, the Agency recommended to the sponsor to conduct an ocular distribution study following intravitreal injection. In this Amendment to the original NDA (SN000BP), the sponsor submitted a ^{14}C-labeled study in New Zealand white rabbits to show the ocular distribution of intravitreally administered triamcinolone acetonide. The results showed that the highest concentrations of radioactivity were in the retina and choroid. The systemic drug levels

were more than 10,000-fold lower than that in retina and not quantifiable (5 ng eq/g) after 4 hours.
The findings of this study do not affect the former recommendation (review dated September 13, 2007) for approval of NDA 22-048.

Conrad H. Chen, Ph.D.
Reviewing Pharmacologist

Concurrence by: Wendelyn Schmidt, Ph.D.
Acting Pharmacology Team Leader

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/s/

Conrad Chen
11/15/2007 03:58:46 PM
PHARMACOLOGIST
The findings of this study do not affect the former recommendation (review dated September 13, 2007) for approval of NDA 22-048.

Wendelyn Schmidt
1/2/2008 08:41:58 AM
PHARMACOLOGIST