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*APPLICATION NUMBER:*  
**22-048/22-223**

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

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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NDA: 22-048/22-223  
Submission Date(s): 24MAY2007  
Brand Name: Triesence™  
Generic Name: Triamcinolone Acetonide Injectable Suspension  
Primary Reviewer: Kimberly L. Bergman, Pharm.D.  
Team Leader: Charles Bonapace, Pharm.D.  
OCP Division: DCP4  
OND Division: DAIOP  
Applicant: Alcon Research, Ltd.  
Relevant IND(s): IND \_\_\_\_\_  
Submission Type; Code: 505(b)(2) application; Priority Review  
Formulation; Strength(s): Triamcinolone Acetonide Injectable Suspension, supplied as 1 mL of 40 mg/mL suspension  
Indication: Treatment of \_\_\_\_\_  
\_\_\_\_\_ sympathetic  
ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions  
unresponsive to topical corticosteroids, \_\_\_\_\_  
\_\_\_\_\_

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**1. EXECUTIVE SUMMARY**

Triamcinolone acetonide is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. Alcon submitted a 505(b)(2) New Drug Application (NDA) for Triamcinolone Acetonide Injectable Suspension (TRIESENCE™) and was granted a priority review. The proposed

indications for Triamcinolone Acetonide Injectable Suspension (TRIESENCE™) are as follows: the treatment of

sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical corticosteroids.

Alcon's Triamcinolone Acetonide Injectable Suspension (TRIESENCE™) is a sterile, non-preserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide supplied in a 1 mL vial. The proposed dose and route of administration for treatment of ophthalmic conditions is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dose of 4 mg (100 µl of 40 mg/mL suspension) as needed over the course of treatment. The proposed dose and route of administration for visualization during vitrectomy is 1 to 4 mg (25 µl to 100 µl of 40 mg/mL suspension) administered intravitreally.

The active component of TRIESENCE™, triamcinolone acetonide, has been previously approved for systemic administration. To support the use of triamcinolone acetonide for the treatment of ophthalmic disorders and diseases and for visualization of vitreous, the current 505(b)(2) NDA for Triamcinolone Acetonide Injectable Suspension includes a meta-analysis of published literature to demonstrate the safety and effectiveness of triamcinolone acetonide for treatment of ophthalmic disorders and diseases and for visualization of vitreous and membranes (Study Report C-06-26). The Applicant did not perform any human pharmacokinetic assessments of TRIESENCE™ injectable ophthalmic suspension. To address the requirement for submission of evidence of in vivo bioavailability, the Applicant submitted published literature documenting the intraocular and systemic exposure of triamcinolone acetonide following intravitreal administration.

### 1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant is acceptable.

### 1.2. Phase IV Commitments

No phase IV commitments are recommended.

### 1.3. Summary of Important Clinical Pharmacology Findings

Ocular and systemic exposure to triamcinolone acetonide following intravitreal injection has been adequately characterized in peer-reviewed publications. Based on published data on aqueous humor pharmacokinetics of triamcinolone acetonide in five elderly patients with macular edema following a single 4 mg intravitreal administration of the currently marketed KENALOG-40 (triamcinolone acetonide suspension), the average model-predicted vitreous C<sub>max</sub> was 4841 ± 2165 ng/mL, AUC<sub>0-t</sub> was 1095 ± 755 ng\*h/mL, and the mean elimination half life was 15.6 ± 8.5 days. Triamcinolone elimination half-life was estimated to be 18.7 ± 5.7 days in the vitreous of non-vitrectomized eyes (following exclusion of one patient who had undergone vitrectomy prior to enrollment).

Sparse pharmacokinetic sampling in patients with age-related macular degeneration, diabetic macular edema, or other reasons for macular edema, demonstrated that systemic exposure to triamcinolone is low or below the limit of quantitation (0.5 ng/mL) following an intravitreal administration of high dose triamcinolone acetonide (20 to 25 mg). Serum concentrations of triamcinolone acetonide were less than 1 ng/ml in all patients studied.

From a Clinical Pharmacology perspective, the requirement for submission of evidence of in vivo bioavailability has been met based on a review of published literature documenting the intraocular and systemic exposure of triamcinolone acetonide following intravitreal administration. No further clinical pharmacology studies are required.

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## 2. QUESTION BASED REVIEW

Since this submission is a 505(b)(2) NDA for a locally administered product relying upon conclusions drawn by the Agency for a previously approved systemically administered product and a meta-analysis of published literature, only relevant questions from the OCP question-based review (QBR) format are addressed below.

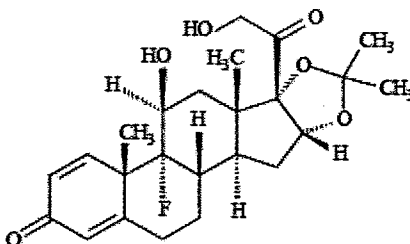
### 2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Triamcinolone acetonide is a synthetic glucocorticoid corticosteroid and is a well characterized USP drug substance. The chemical structure and physical-chemical properties of triamcinolone are shown below:

**Structural Formula:**  $C_{24}H_{31}FO_6$

**Chemical Structure:**



**Chemical Name:**

[

]

(2) 9-Fluoro-11 $\beta$ ,16 $\alpha$ ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17- acetal with acetone

**Compendial Name:** Triamcinolone Acetonide (USP)

**USAN:** Triamcinolone Acetonide

**Company or Laboratory Code:**  
AL-938 (Alcon)

**CAS Registry Number:**  
76-25-5

**Molecular Weight:** 434.50

Triamcinolone Acetonide Injectable Suspension (Triamcinolone Acetonide Injection) is a sterile, non-preserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide. The objective of the pharmaceutical development of Triamcinolone Acetonide Injectable Suspension was to develop a terminally sterilized, stable, unpreserved, pyrogen-free unit dose parenteral (injectable) product for intra-ocular use which is pharmaceutically and therapeutically equivalent to KENALOG®-40 (NDA 14-901). The concentration of 40 mg/mL of triamcinolone acetonide is the same as that in KENALOG-40. The proposed drug product was developed with no preservative and reduced concentrations of the wetting agent and the suspending agent and with the addition of essential ions, tonicity agent and buffering agents, compared to KENALOG-40.

The quantitative composition of Triamcinolone Acetonide Injectable Suspension drug product is shown in the following table (Table 2.2-1):

Table 2.2-1 Composition of Triamcinolone Acetonide Injection

Component	% w/v	Function	Compendial Status
Triamcinolone Acetonide	4.0	Active	USP
Polysorbate 80	0.015		NF
Carboxymethylcellulose Sodium	0.5		USP
Sodium Chloride			USP
Potassium Chloride			USP
Calcium Chloride (Dihydrate)			USP
Magnesium Chloride (Hexahydrate)			USP
Sodium Acetate (Trihydrate)			USP
Sodium Citrate (Dihydrate)			USP
Sodium Hydroxide and/or Hydrochloric Acid			NF
Water for Injection			USP

2.1.2. *What is the proposed mechanism of drug action and therapeutic indication?*

Triamcinolone acetonide is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. Corticosteroids interact with specific receptor proteins in target tissues to regulate the expression of corticosteroid-responsive genes, thereby changing the levels and array of proteins synthesized by the various target tissues.

2.1.3. *What is the proposed dosage and route of administration?*

For treatment of ophthalmic conditions, the proposed use of TRIESENCE™ is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dosing of 4 mg (100 µl of 40 mg/mL suspension) as needed over the course of treatment.

For visualization during vitrectomy, the proposed dose of TRIESENCE™ is 1 to 4 mg (25 µl to 100 µl of 40 mg/mL suspension) administered intravitreally.

## 2.2. General Clinical Pharmacology

### 2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

No clinical pharmacology studies were submitted in this NDA.

To support dosing claims, the Applicant submitted a meta-analysis of published literature to demonstrate the safety and effectiveness of triamcinolone acetonide for treatment of ophthalmic disorders and diseases and for visualization of vitreous and membranes (Study Report C-06-26). The report contains published data from 300 peer-reviewed articles, the majority of which were prospectively designed trials (68.7%). The dose range studied was triamcinolone acetonide injectable suspension 1 to 4 mg administered intravitreally in both single and multiple injections. Further information regarding this meta-analysis can be found in the Medical Officer's review for NDA 22-048.

### 2.2.2. What are the PK characteristics of the drug?

The Applicant submitted six publications with ocular and systemic pharmacokinetic information, two of which support Clinical Pharmacology statements in the proposed label. In these two studies, triamcinolone acetonide concentrations in serum, aqueous humor, and vitreous humor following intravitreal or subtenon administration have been quantified. The two studies supporting labeling statements were the subject of this Office of Clinical Pharmacology review and are as follows:

1. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB, Miller M. *Ophthalmology* 2003 Apr;110(4):681-686.
2. Serum levels of triamcinolone acetonide after intravitreal injection. Degenring RF, Jonas JB. *Am J Ophthalmol* 2004 Jun;137(6):1142-1143.

#### 2.2.2.1. Ocular Exposure Following Intravitreal Administration

Beer and colleagues investigated the intraocular pharmacokinetics of triamcinolone acetonide following a single intravitreal injection (*Ophthalmology* 2003 Apr;110(4):681-686). Aqueous humor pharmacokinetics of triamcinolone acetonide were assessed in one eye each from five elderly patients with macular edema following a single 4 mg intravitreal administration of the currently marketed KENALOG-40 (triamcinolone acetonide suspension).

Following a single intravitreal injection of a 4 mg dose of triamcinolone acetonide, mean aqueous humor concentrations of triamcinolone acetonide were measurable (lower limit of quantitation of 10 ng/mL) in all 5 eyes at all time points (five samples per patient) and ranged from 88 ng/mL (Day 31) to 5410 ng/mL (Day 1). Mean triamcinolone acetonide aqueous C<sub>max</sub> (observed on Day 1, the first sampling time point) was 3380 ± 1621 ng/mL following intravitreal administration of KENALOG-40. Based on two-compartmental modeling, the average model-predicted vitreous C<sub>max</sub> was 4841 ± 2165 ng/mL, AUC<sub>0-t</sub> was 1095 ± 755 ng·h/mL, and the mean elimination half life was 15.6 ± 8.5 days. Triamcinolone elimination half-life was estimated to be 18.7 ± 5.7 days in the vitreous of non-vitrectomized eyes (following exclusion of one patient who had undergone vitrectomy prior to enrollment).

#### 2.2.2.2. Systemic Exposure Following Intravitreal Administration

Degenring and Jonas evaluated serum concentrations of triamcinolone acetonide after intravitreal high-dose injection in a prospective, interventional case series study (*Am J Ophthalmol* 2004 Jun;137(6):1142-1143). Serum drug concentrations were measured via sparse sampling in 20 patients with age-related macular degeneration (N = 14), diabetic macular edema (N = 4), or other reasons for macular edema (N = 2) following an intravitreal high dose (20 to 25 mg) administration of triamcinolone acetonide injection. Samples (one sample per patient) were obtained before and 4 to 92 days after the intravitreal injection.

Following an intravitreal high dose of triamcinolone acetonide, triamcinolone acetonide concentrations were below the limit of quantitation (< 0.5 ng/mL) in the serum of 18 patients (90%). In both patients exhibiting measurable serum concentrations, triamcinolone acetonide concentrations were less than 1 ng/mL at 5 and 7 days following intravitreal injection, respectively.

From a Clinical Pharmacology perspective, the requirement for submission of evidence of in vivo bioavailability has been met based on a review of published literature documenting the intraocular and systemic exposure of triamcinolone acetonide following intravitreal administration.

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### 3. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear highlighted in ***bold italicized underlined type*** and deleted text in strike-through font).

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       § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## 4. APPENDICES

### 4.1. Individual Study Reviews

#### 4.1.1. Published Literature Reports

***Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB, Miller M. Ophthalmology 2003 Apr;110(4):681-686.***

Objective:

To describe the intraocular pharmacokinetics of triamcinolone acetonide after a single intravitreal injection.

Methods:

Aqueous humor pharmacokinetics of triamcinolone acetonide were assessed in 5 elderly patients (3 males and 2 females, 71 to 88 years of age) with macular edema following a single intravitreal administration (4 mg) of KENALOG-40. Of the 5 patients, one had undergone a vitrectomy 4 months prior to inclusion in the study. Serial aqueous humor samples were obtained from the 5 patients (5 eyes) via an anterior chamber paracentesis on Days 1, 3, 10, 17 and 31 following the intravitreal administration. Triamcinolone acetonide aqueous concentrations were measured using high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) with a limit of quantification of 10 ng/mL. Indirect ophthalmoscopy was also used for visual inspection of drug particles in the vitreous following the single administration, as evidenced by white crystalline clumps. Intraocular pharmacokinetics of triamcinolone acetonide was characterized using both noncompartmental and compartmental models.

Results:

Five eyes of 5 participants completed the study. Indirect ophthalmoscopy showed visible triamcinolone acetonide particles in the vitreous of all 5 eyes 31 days after drug administration, as evidenced by white crystalline clumps. Drug particles were visible in the vitreous for as long as 101 days in one patient (Patient Number 5), 94 days in one patient (Patient Number 3), and 80 days in one patient (Patient Number 4). No visible triamcinolone crystals were seen in the anterior chamber in any of the study eyes at any time during the study.

Aqueous concentrations of triamcinolone acetonide were measurable ( $> 10$  ng/mL) in all 5 eyes at all time points. Variability in triamcinolone concentrations across subjects was high, as demonstrated by the individual concentration-time plots displayed in Figure 1. Mean triamcinolone acetonide aqueous  $C_{max}$  (observed on Day 1, the first sampling time point) was  $3380 \pm 1621$  ng/mL following intravitreal administration of KENALOG-40. Triamcinolone aqueous concentration-time data for each patient were best described by a two-compartment model with bolus input and first order output following the single intravitreal administration. Population parameters showed large intrasubject variation. The average model-predicted vitreous  $C_{max}$  was  $4841 \pm 2165$  ng/mL, corresponding to maximum triamcinolone acetonide concentrations in the vitreous immediately following intravitreal administration. The average  $AUC_{0-t}$  was  $1095 \pm 755$  ng\*h/mL and the mean elimination  $t_{1/2}$  was  $15.6 \pm 8.5$  days. One outlier was identified; for Patient Number 2, who had undergone vitrectomy prior to enrollment, the terminal elimination  $t_{1/2}$  was 3.2 days. Exclusion of this outlier did not have a significant effect on the interpretation of descriptive statistics (mean  $t_{1/2}$  excluding Patient Number 2 was  $18.7 \pm 5.7$  days).

Figure 1.

Spaghetti Plot of Individual Intravitreal Triamcinolone Concentrations After a Single Intravitreal Triamcinolone Acetonide Injection (4 mg)

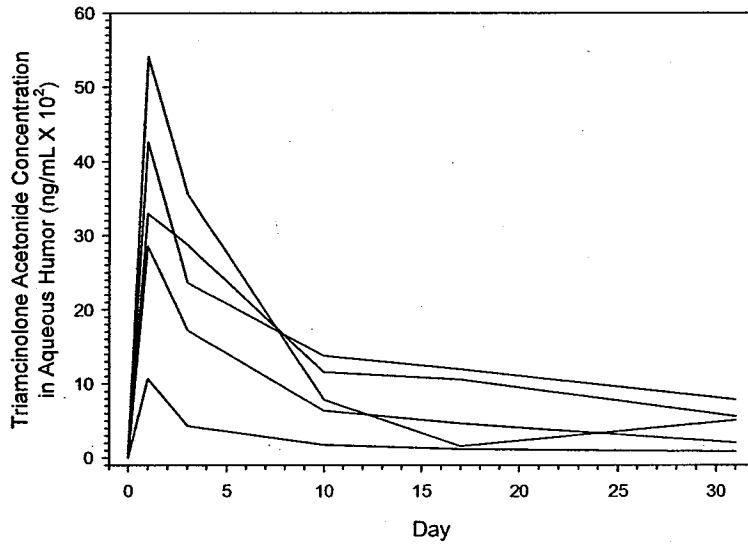


Table 1.

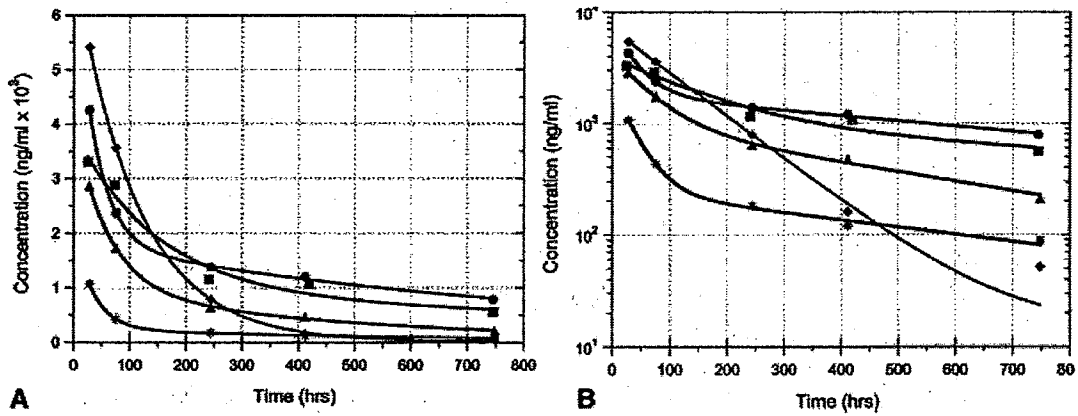
Ocular Pharmacokinetic Parameters of Triamcinolone Acetonide Following Single Intravitreal Administration (4 mg) of KENALOG-40

Patient No.	C <sub>max</sub> (ng/mL)*	AUC <sub>0-4</sub> (ng*h/mL)	t <sub>1/2</sub> (h)	r <sup>2</sup>
1	4040	684	352	0.9998
2	6932	781	76	0.9999
3	7202	1869	635	0.9999
4	2151	231	465	0.9998
5	3880	1911	341	0.9943
Mean	4841	1095	374	0.9987
SD	2165	755	204	0.0025

\*C<sub>max</sub> is the y-intercept for the PK model corresponding to vitreous drug concentrations immediately after injection.

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Figure 2. Intravitreal Triamcinolone Concentrations After a Single Intravitreal Triamcinolone Acetonide Injection (4 mg)



A, Linear Scale; B, Logarithmic Scale

Symbols represent individual patients; lines represent two-compartment model derived curves.

Conclusions:

Based on the elimination  $t_{1/2}$  of  $18.7 \pm 5.7$  days and assuming 97% of triamcinolone is cleared from the vitreous after 5 half lives, drug concentrations in the vitreous of non-vitreotomized eyes should last approximately 90 days following a single intravitreal 4-mg dose. However, in patients, who have undergone vitrectomy, triamcinolone concentrations are predicted to undergo more rapid elimination from the vitreous.

Reviewer Assessment:

Published data from this study is acceptable from an Office of Clinical Pharmacology Perspective.

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***Serum levels of triamcinolone acetonide after intravitreal injection. Degenring RF, Jonas JB. Am J Ophthalmol 2004 Jun;137(6):1142-1143.***

**Objective:**

To evaluate serum levels of triamcinolone acetonide after intravitreal high-dose injection.

**Methods:**

In this prospective, interventional case series study, serum drug concentrations were measured in 20 patients with age-related macular degeneration (N = 14), diabetic macular edema (N = 4), or other reasons for macular edema (N = 2) following an intravitreal high dose (20 to 25 mg) administration of triamcinolone acetonide injection. Sparse blood samples (one sample per patient) were obtained before and 4 to 92 days after the intravitreal injection. Triamcinolone acetonide serum concentrations were measured using HPLC-MS/MS with a limit of quantification of 0.5 ng/mL.

**Results:**

In 18 patients (90%), triamcinolone acetonide concentrations were BLOQ (< 0.5 ng/mL); Triamcinolone acetonide was quantifiable in 2 patients (10%). One patient, who never had a previous triamcinolone injection, had a concentration of 0.8 ng/mL at 7 days after the injection. A second patient, who had received 4 previous intravitreal injections of triamcinolone acetonide at 12, 17, 24, and 29 months before inclusion in the study, had a concentration of 0.5 ng/mL at 5 days after dosing.

These results indicated that serum concentrations of triamcinolone are low following an intravitreal administration of triamcinolone acetonide high dose (20 to 25 mg). Since the physiologic cortisol serum concentrations are typically range from 70 ng/mL to 80 ng/mL in healthy elderly subjects, the low serum concentrations of triamcinolone (0.5 to 0.8 ng/mL) observed in two patients would be unlikely to exert pharmacologic effects even though triamcinolone has a higher potency than cortisol/hydrocortisone.

**Conclusions:**

Based on the results of this study, systemic side effects from a therapeutic intravitreal dose of triamcinolone acetonide are not expected.

**Reviewer Assessment:**

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