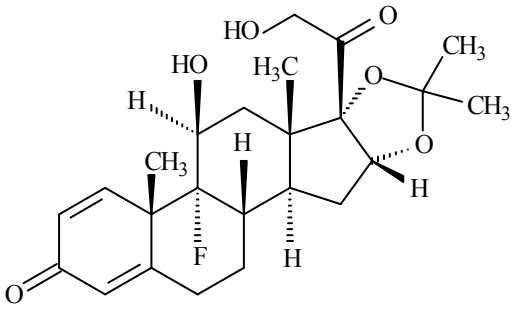
# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA 22-048 / 22-223 |
| Submission Number | 000 |
| Submission Code | Original |
| Letter Date | May 24, 2007 |
| Stamp Date | May 29, 2007 |
| PDUFA Goal Date | November 29, 2007 |
| Reviewer Name | Martin P. Nevitt, M.D., M.P.H. |
| Review Completion Date | Oct. 24, 2007 |
| Established Name | triamcinolone acetonide injectable suspension, 40 mg/ml |
| (Proposed) Trade Name | Triesence |
| Therapeutic Class | corticosteroid |
| Applicant | Alcon, Inc. |
| Priority Designation | P |
| Formulation | Active ingredient: triamcinolone acetonide |
| Structure | $C_{24}H_{31}FO_6$ |



| | |
|---|---|
| (Proposed) Dosing Regimen | **Dosage for Treatment of Ophthalmic Conditions:**<br>The initial recommended dose of TRIESENCE™ is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dosage as needed over the course of treatment.<br><br>**Dosage for Visualization During Vitrectomy:**<br>The recommended dose of TRIESENCE™ is 1 to 4 mg (25 µl to 100 µl of 40 mg/mL suspension) administered intravitreally. |
| (Proposed) Indication | [redacted]<br><br>arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids; [redacted] and for visualization of vitreous [redacted] d vitrectomy |
| (Proposed) Intended Population | [redacted] |

sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids;

vitrectomy for visualization

vitreous

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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-048 / 22-223 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Triescence (triamcinolone acetonide injectable suspension) for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids, and for visualization of the vitreous during vitrectomy.

There are no recommendations for additional postmarketing studies.

## 1.2 Recommendation on Postmarketing Actions

### Risk Management Activity

There are no proposed risk management actions.

### Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

### Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

## 1.3 Summary of Clinical Finding

### Brief Overview of Clinical Program

Triescence (triamcinolone acetonide injectable suspension) is a sterile, terminally sterilized, non-preserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide which is pharmaceutically and therapeutically equivalent to a marketed product

KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ). The applicant is filing a 505(b)(2) New Drug Application (NDA) for triamcinolone acetonide injectable suspension for the treatment of [redacted] sympathetic ophthalmia, temporal arteritis, uveitis, ocular [redacted] esponsive to topical steroids; [redacted] visualization of vitreous [redacted] during vitrectomy

Triamcinolone acetonide injectable suspension has been developed with no preservative. The preservative benzyl alcohol was removed since this will be a single-use, intravitreal dosage form. The concentration of 40 mg/mL of triamcinolone acetonide is the same as that in KENALOG-40.

USP monographs for the drug substance, triamcinolone acetonide, and for the product, triamcinolone acetonide injectable suspension exist. The drug product monograph does not mention preservative and hence can be applied to both Kenalog-40 and Triesence.

Glucocorticoids such as dexamethasone and triamcinolone have been utilized for decades for the treatment of ocular inflammation. Triamcinolone acetonide has been used specifically to treat posterior segment diseases that are associated with inflammation, enhanced vascular permeability and pathologic angiogenesis, due to its depot properties when administered locally to the eye. Consequently, local delivery of triamcinolone acetonide (eg, intravitreal or subTenon's injection) is being used in humans for the treatment of exudative age-related macular degeneration (choroidal neovascularization) and macular edema associated with diabetes mellitus, retinal branch vein or artery occlusion, and uveitis. Although the use of a glucocorticoids in these conditions has been purported to provide efficacy, a variety of ocular complications are found following the use of these agents, such as ocular hypertension or glaucoma and cataract formation.

Triamcinolone acetonide is also being used to enhance the visualization of vitreous [redacted] during vitrectomy procedures. The applicant has developed several formulations of triamcinolone that are potentially viable for intraocular use. In rabbit studies, these formulations were found to perform in a similar clinical manner to currently marketed formulations not intended for intraocular use, e.g. KENALOG®-40.

There are no currently approved drug therapies for [redacted]

There is over a 40 year history of use of the active ingredient, triamcinolone acetonide, in the United States (marketed by Bristol-Myers, Squibb, Princeton, NJ, as KENALOG-40) with adequate demonstration of safety and efficacy for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory unresponsive to topical corticosteroids.

## Efficacy

The application supports the effectiveness of Triesence (triamcinolone acetonide injectable suspension) for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and the visualization of the vitreous during vitrectomy.

The major sources of clinical data in support of efficacy for triamcinolone acetonide utilized in this review include:

- Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report)
- Data from the Clinical trial C-05-62: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery

## Safety

There is over a 40 year history of use of the active ingredient, triamcinolone acetonide, in the United States (marketed by Bristol-Myers, Squibb, Princeton, NJ, as KENALOG-40) with adequate demonstration of safety and efficacy for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammation unresponsive to topical corticosteroids.

The data submitted for the assessment of safety for triamcinolone acetonide is adequate. The safety and efficacy effects seen with this product are class effects related to ophthalmic steroids.

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

## Dosing Regimen and Administration

For the treatment of ophthalmic conditions the initial recommended dose of Triescence is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dosage of 4 mg (100 µl of 40 mg/mL suspension) as needed over the course of treatment.

For visualization during vitrectomy the recommended dose of Triescence is 1 to  mg (100 µl of 40 mg/mL suspension) administered intravitreally.

Drug-Drug Interactions

Specific drug interaction studies are not reported. No additional adverse drug-drug interactions were noted in the literature review.

## Special Populations

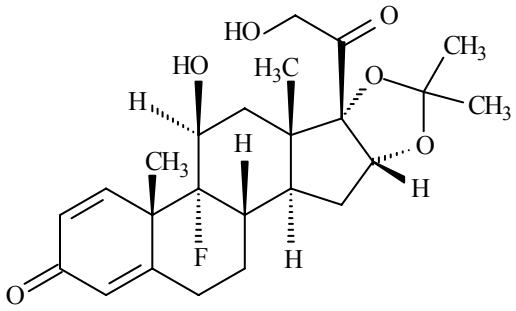
No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established use of triamcinolone acetonide.

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Product Information

| | |
|---|---|
| **Established Name** | triamcinolone acetonide injectable suspension, 40 mg/ml |
| **(Proposed) Trade Name** | Triesence |
| **Therapeutic Class** | Corticosteroid |
| **Formulation** | $C_{24}H_{31}FO_6$ |



**Composition of triamcinolone acetonide injection (FID* 110300)**

| 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 NF |
| Water for Injection | | | USP |

* FID = Formulation Identification Number

**Reviewer's comments:**

*The proposed formulation of triamcinolone acetonide injection is preservative-free and does not contain benzyl alcohol, a preservative used in KENALOG 40 another formulation of injectable triamcinolone acetonide. The preservative benzyl alcohol which has been associated with adverse events such as sterile endophthalmitis has been removed since this proposed formulation will be used as a sterile, single-use, intravitreal dosage form.*

## 2.2 Currently Available Treatment for Indications

Kenalog-40 is approved and marketed for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory unresponsive to topical corticosteroids.

There are no currently approved drug therapies for

## 2.3 Availability of Proposed Active Ingredient in the United States

Triamcinolone acetonide (TA) is a synthetic glucocorticoid corticosteroid and is a well characterized USP drug substance. Glucocorticoids (such as dexamethasone and triamcinolone acetonide) have been utilized for decades for the treatment of ocular inflammation.

Triesence (triamcinolone acetonide injectable suspension) is a sterile, terminally sterilized, non-preserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide which is pharmaceutically and therapeutically equivalent to a marketed product KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ). The concentration of 40 mg/mL of triamcinolone acetonide is the same as that in KENALOG-40.

USP monographs for the drug substance, triamcinolone acetonide and for the product, triamcinolone acetonide injectable suspension, exist. The drug product monograph does not mention preservative and hence can be applied to both Kenalog-40 and Triesence.

Triamcinolone acetonide is also approved as a nasal spray (NDA 20-784, Nasacort HFA Nasal Aerosol).

## 2.4 Important Issues with Pharmacologically Related Products

The safety and efficacy effects seen with this product are class effects related to ophthalmic steroids.

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

## 2.5 Presubmission Regulatory Activity

A Pre-NDA meeting was scheduled for October 3, 2006, for NDA 22-048 (PIND 73,462). Based on correspondence for that meeting, the FDA confirmed that a literature based clinical development program in conjunction with the cross-reference of NDA 14-901 (KENALOG® - 40) would be acceptable to support the fileability of the proposed indications provided:

- For an indication for [redacted] visualization during vitrectomy, the Agency would expect the literature and referenced new drug applications to demonstrate a favorable risk/benefit ratio based on adequate and well controlled studies. The specific information to be collected from the literature sources should include study design, patient demographics, disease characteristics, ocular diagnoses, treatments, routes of administration and dosage

information. The concentration and frequency of dosing of the drug product used in the clinical studies should be at least as high as, and as frequent as, that proposed for marketing.

- Substantial evidence of efficacy and safety should come from adequate and well controlled studies. The study design, endpoints, inclusion/exclusion criteria, the follow-up period, etc. should be consistent with the regulatory guidelines.

On May 29, 2007, Alcon submitted a 505(b) (2) application cross-referencing information from NDA 14-901 (KENALOG® -40) requesting a 6 month priority review. For NDA 22-048 a priority review was granted since there are no currently approved drug therapies for the proposed indications for [redacted]; or for the visualization of the vitreous [redacted] w period was set for the previously approved indications of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical steroids.

NDA 22-048 / 22-223 is supported by Clinical study report C-06-26 and Clinical trial C-05-62. Clinical study report C-06-26 is a meta-analysis of published peer reviewed literature that is provided to support the safety and effectiveness of triamcinolone acetonide in the treatment of ophthalmic disorders and diseases and for use in ocular surgery to enhance visualization of vitreous [redacted]. To achieve this goal, available peer reviewed literature was critically analyzed in accordance with the clinical protocol for study C-06-26.

Additionally to support the indication of visualization during vitrectomy, Clinical trial C-05-62 (Title: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery) was conducted to evaluate the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension when used for visualization during pars plana vitrectomy with or without membrane removal.

## 2.6 Other Relevant Background Information

Triamcinolone Acetonide Injectable Suspension (KENALOG®-40, NDA 14-901) with a concentration of 40 mg/mL of triamcinolone acetonide has been previously approved for the following ophthalmic indications: sympathetic ophthalmia, temporal arteritis, uveitis and ocular conditions unresponsive to topical steroids.

Triamcinolone acetonide is also approved as a nasal spray (NDA 20-784, Nasacort HFA Nasal Aerosol).

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## 3.1 CMC (and Product Microbiology, if Applicable)

NDA 22-048/22-223 is recommended for approval from the standpoint of product quality microbiology. There are no microbiology deficiencies identified. Appropriate language stressing the use of aseptic techniques during administration is provided in the package insert. The blister package label includes the dose, the word "sterile" and the phrase "single use."

## 3.2 Animal Pharmacology/Toxicology

Review pending.

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## 4.1 Sources of Clinical Data

The major sources of clinical data utilized in this review include:

- Literature references citing the use of the product Triamcinolone Acetonide Injectable Suspension in Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report)
- Data from Clinical trial C-05-62 (Title: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)

Clinical Study Report C-06-26 is a meta-analysis based on published data from 300 peer-reviewed articles, of which 299 (out of 1,272 considered) met the criteria set forth in the protocol (refer to section 6.1.a for flowchart of criteria). These 299 articles describe the use of triamcinolone acetonide for the treatment of ophthalmic disorders and diseases and for visualization of vitreous during vitrectomy.

Clinical trial C-05-62, "Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery,"

evaluated the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension when used for visualization during pars plana vitrectomy with or without membrane removal. The primary efficacy consisted of the evaluation of the visualization of posterior segment structures in pars plana vitrectomy before and after instillation of triamcinolone acetonide. Safety variables include intraocular pressure, slit-lamp assessment of anterior segment inflammation (aqueous cells, aqueous flare, and corneal edema), and dilated fundus assessment of vitreous haze, retina, macula, choroid and optic nerve. Patients were examined preoperatively, in addition to Days 1 and 7 following surgery.

## 4.2 Tables of Clinical Studies

**Listing of Clinical Studies**

| Study | Study Title | Study Design | Test Product | Enrolled | Healthy Subjects or Diagnosis of Patients |
|---|---|---|---|---|---|
| C-06-26 Literature references | Meta-analysis of published peer reviewed literature to support the safety and effectiveness of triamcinolone acetonide in the treatment of ophthalmic disorders and diseases and for use in ocular surgery to enhance visualization of vitreous and membranes | Meta-analysis of published literature (includes prospective and retrospective studies including masked and placebo controlled studies) | Typically 1-4 mg. administered intravitreally | Literature covering 13,983 patients | Patients requiring treatment [redacted] during vitrectomy |
| C-05-62 | Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery | Prospective, multi-center observer-masked | Sterile, injectable suspension, preservative-free | 66 subjects to obtain 60 evaluable subjects | For visualization [redacted] during vitrectomy |

**Reviewer's Comments:**

*Substantial evidence of efficacy and safety should come from adequate and well controlled studies. The study design, endpoints, inclusion/exclusion criteria, the follow-up period, etc. should be consistent with the regulatory guidelines.*

*The data from Clinical Study Report C-06-26 and Clinical Study C-05-62 was reviewed for each indication in Section 6.1.4 (Efficacy findings) to determine their consistency with the regulatory guidelines for approval.*

*For efficacy the endpoints recommended are statistically significant differences in a measurement of visual function (e.g., visual acuity, visual field, etc.) at a follow-up period deemed clinical significant for each indication. Efficacy for visualization was based on a 5 point scale ("0 not visible," to "4 clearly delineated") for the relevant posterior segment structure graded by an independent masked reader.*

*The majority of the studies reported best corrected visual acuity measurements (BCVA) and additionally some also reported optical coherence tomography (OCT) measurements of retinal / macular thickness. The agency considers a 3-line change in visual acuity to be clinically significant. OCT has not been correlated to visual function and is not recommended as a primary endpoint.*

*The recommended follow-up period for the primary efficacy endpoint(s) are:*

*24 hours; immediate intraoperative (visualization during surgery) results with 24 hour and 1 week follow-up.*

## 4.3 Review Strategy

The major sources of clinical data utilized in this review include:

- Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report)
- Clinical trial C-05-62: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery.

### 4.4 Data Quality and Integrity

For Clinical study report C-06-26, the reference literature reports articles cited in this review are representative of the published literature. The literature search queried published articles from 1966 to February 14, 2007. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

Clinical trial C-05-62: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery was conducted in 2007. There is no evidence that this study was not conducted in accordance with acceptable clinical ethical standards.

There were no Division of Scientific Investigations (DSI) audits. The case report forms for Clinical study report C-06-26 and Clinical trial C-05-62 were provided by the applicant, and these were reviewed for completeness and quality. Videos of pre and post instillation of the visualization during surgery were also reviewed.

### 4.5 Compliance with Good Clinical Practices

There is no evidence that these studies were not conducted in accordance with acceptable clinical ethical standards.

### 4.6 Financial Disclosures

For Clinical study report C-06-26 no clinical studies have been conducted. Consequently, no completed certification and disclosure forms were provided.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

Review pending.

### 5.2 Pharmacodynamics

Review pending.

### 5.3 Exposure-Response Relationships

There is adequate clinical experience with the proposed drug product, Triamcinolone Acetonide Injectable Suspension to determine its safety. For the safety and efficacy of the product for each indication refer to sections 6 and 7, respectively.

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

The proposed indications are:

- 
- 
- 
- 
- for visualization of the vitreous during vitrectomy, and
- for sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unresponsive to topical steroids.

### 6.1.1 Methods

The major sources of clinical data utilized in this review include:

- Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report)
- Data from the Clinical trial C-05-62: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery

### 6.1.2 General Discussion of Endpoints

Regarding the choice of endpoints for the proposed indications of 

the literature references from the meta-analysis (Clinical study report C-06-26) measure best corrected visual acuity at follow-up. Best corrected visual acuity data was reported using various eye charts with their slightly different recording measurements. Below is the method that was used to covert all measurements to logMAR visual acuity:

**Algorithm used for Converting from Visual Acuity Data to logMAR Units**

| If reported unit for visual acuity was: | The conversion to logMAR was*: |
|---|---|
| Decimal | $-\log_{10}$(value) |
| ETDRS Letters | (85 – value) x 0.02 |
| logMAR Units | value |
| Snellen: 20 / | $-\log_{10}$(20/value) |
| Snellen: 6 / | $-\log_{10}$(6/value) |

* value = the reported visual acuity value in its original unit.

Best- or current-corrected visual acuity data were collected from patients using ETDRS / logMAR, decimal, or Snellen charts and subsequently converted to logMAR equivalents. The CRF was designed to capture visual acuity data presented in the units reported in the individual papers. The data could be reported either by-visit or as a last mean follow-up (LMFU). Visual acuity outcomes were summarized in this report as either mean visual acuity (logMAR scale), mean change from baseline in visual acuity, and the percentage of patients with a visual acuity improvement of at least 2 lines (10 letters). In visualization studies, the primary efficacy assessment pertained to whether the injected triamcinolone acetonide was useful to the surgeon for visualization during vitrectomy.

Clinical study report C-06-26 also contained information for visualization during vitreoretinal surgery. The literature references from the meta-analysis cite whether triamcinolone acetonide was useful for visualization during surgery. Additionally, Clinical trial C-05-62 (Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery) was conducted to evaluate the safety and efficacy for visualization during surgery.

### 6.1.3 Study Design

Clinical study report C-06-26 provides a meta-analysis of published peer reviewed literature to support the safety and effectiveness of triamcinolone acetonide in the treatment of ophthalmic disorders and diseases and for use in ocular surgery to enhance visualization of vitreous . Comments on Study design as they pertain to literature references for efficacy are found in Section 6.1.4.

Clinical trial C-05-62, (Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)

evaluated the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension when used for visualization during pars plana vitrectomy with or without membrane removal.

**Reviewer's Comments:**

*Clinical Study Report C-06-26, a meta-analysis, and Clinical trial C-05-62 were reviewed for each indication in Section 6.1.4 (Efficacy findings) and in Section 7.1 (Safety) to determine their consistency with the regulatory guidelines for approval.*

# CLINICAL PROTOCOLS

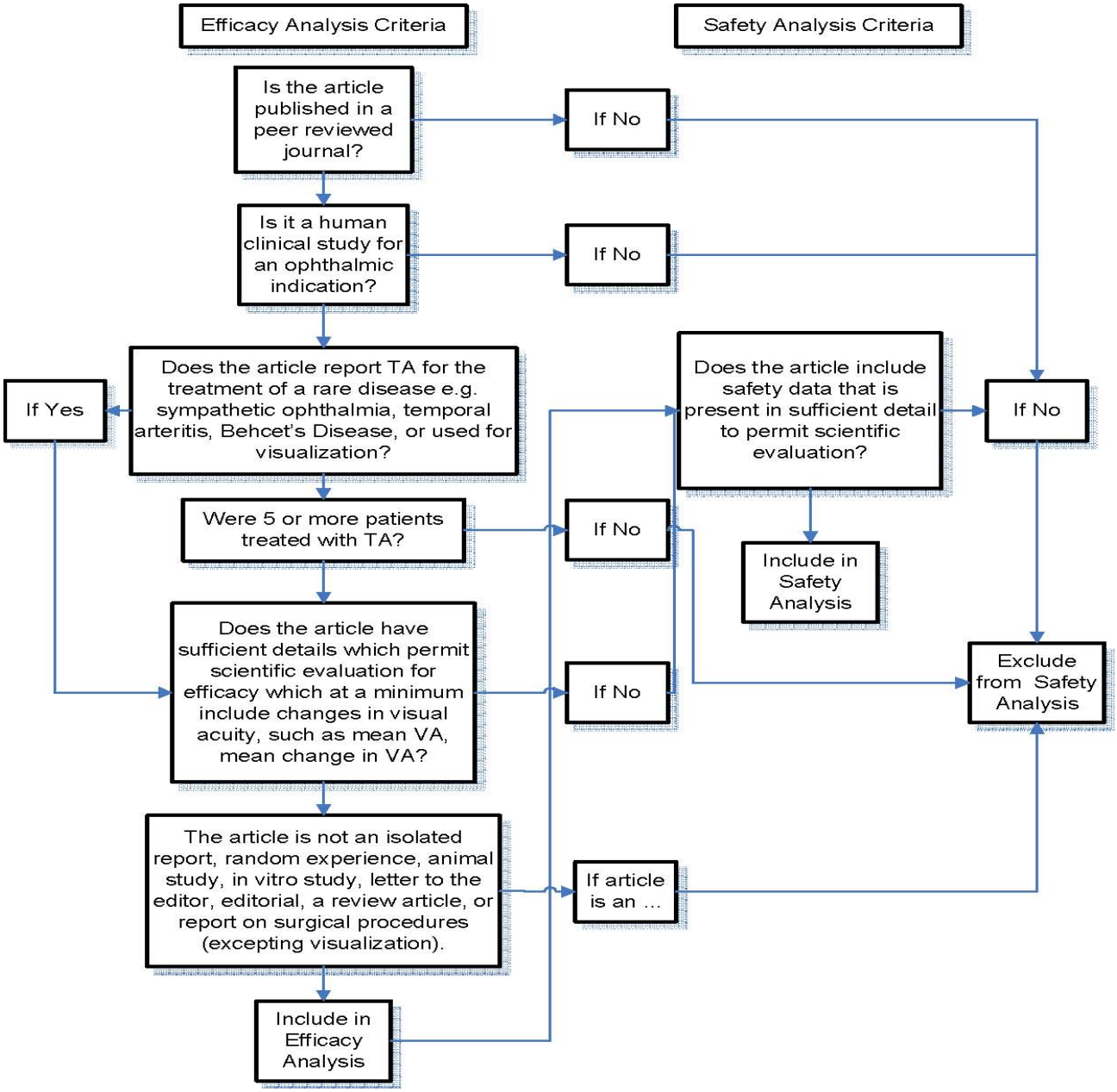
## Protocol: Clinical Study Report C-06-26
## A meta-analysis

**Inclusion / Exclusion Criteria**

The efficacy and safety data sets included the following:

Published literature dating from 1966 (Medline 1966; Embase from 1974) to February 14, 2007.

- Studies were retrospective and prospective.
- The flowchart presented below shows the primary inclusion/exclusion criteria for article selection for the efficacy and safety data sets.




Additional Efficacy Criteria Articles designated for efficacy were adequate and well designed according to the following definitions:

- There was a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol contained a description of the proposed methods of analysis, and the study report contains a description of the methods of analysis ultimately used.

- The study used a design that permitted comparison with a control to provide a quantitative assessment of drug effect.

Additional Safety Criteria Articles designated for safety were those in which triamcinolone acetonide was administered and safety assessments were reported in sufficient detail to permit scientific evaluation.

In total, the 300 articles report on treatment or observation of 13,983 patients and 18,653 eyes across a variety of diseases, indications, and therapies.

**Reviewer's Comments:**

*The meta-analysis contains articles with many variables:*

- *The route of drug administration varied from intravitreal to periocular routes (Sub-Tenon's or retrobulbar)*
- *Dosing ranged from 1 to 40 mg of triamcinolone acetonide*
- *Dose administration varied from single to multiple doses and may have been prior to, during, of after a surgery*
- *Studies may have been masked (single or double masked) or unmasked*
- *Measurement of the primary endpoint (best corrected visual acuity) was reported using different eye charts whose values were then converted to logMAR units*
- *There were various follow-up periods reported by visit or by LMFU (last mean follow-up)*

## Protocol: Clinical Trial C-05-62

**(Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)**

The objective of this study was to evaluate the safety and efficacy of preservative-free triamcinolone acetonide sterile suspension when used for visualization during pars plana vitrectomy with or without membrane removal.

**Principle Investigators and Subjects Enrolled**

| Principle Investigator | Location | Subjects Enrolled |
|---|---|---|
| Thomas Bochow M.D. | Tyler, TX | 11 |
| Todd Schneiderman M.D. | Silverdale, WA | 9 |
| Prema Abraham M.D | Rapid City, SD | 8 |
| S. Lee M.D. | Abilene, TX | 15 |
| H. Michael Lambert, M.D. | Houston, TX | 8 |
| David Dyer, M.D. | Shawnee Mission, KS | 11 |

## Reviewer's comments:

*It is preferred to have at least 10 subjects per center to allow for interaction analysis.*

**Inclusion Criteria:**

1. Male or female patients of any race who are 18 years of age or older (see specific exclusions for a female of childbearing potential below);
2. Patients who are willing to comply with follow-up, able to follow instructions and are able to understand and sign an informed consent form that has been approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC);
3. Patients who are planning to undergo pars plana vitrectomy with or without membrane removal (e.g., epiretinal membrane peel, internal limiting membrane peel, macular hole repair, etc.).

**Exclusion Criteria:**

1 Hypersensitivity to triamcinolone acetonide, any of its components, or other steroid medications (includes steroid-responders);
2 Previous vitrectomy in the study eye;
3 Elevated intraocular pressure (IOP > 21 mmHg) in the study eye at the baseline examination;
4 Any abnormality preventing reliable tonometry in either eye;
5 The presence of any clinically relevant change immediately prior to surgery, compared to baseline, in the anterior or posterior segment examination based upon an assessment by the investigator;
6 Previous intraocular posterior segment surgery in the study eye within 90 days of the preoperative baseline visit;
7 Silicone oil currently within the study eye;
8 Use of any other investigational product during the surgical procedure;
9 Other agents used for intraocular visualization (e.g., indocyanine green, trypan blue, Kenalog®-40);
10 A history of chronic, or recurrent inflammatory eye disease in the study eye (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis);
11 A visually non-functional fellow eye with best corrected Snellen visual acuity worse than 20/200 (equivalent to a logMAR visual acuity worse than 1.0);
12 Participation in any other clinical study within 30 days before the baseline visit or at any time during study participation;
13 Enrollment of the second (fellow) eye of a patient currently or previously enrolled into this study. (Each patient will have only one eye enrolled into the study); or
14. Females of childbearing potential (those who are not surgically sterilized or post menopausal) are excluded from participating in the study if they meet any one of the following conditions:
    a. Currently pregnant,

b. A positive urine pregnancy test result at the baseline examination,
c. An intention to become pregnant during the study period,
d. Currently breast-feeding, or
e. Not using highly effective birth control measures (oral contraceptives, implanted or injected hormonal contraceptives, spermicide in conjunction with a barrier such as a condom or diaphragm, or IUD).

**Study Design:**

This study is a multi-center, observer-masked study of preservative-free triamcinolone acetonide sterile injectable suspension. Patients will receive unpreserved triamcinolone acetonide as a surgical adjunct for enhancing visualization of transparent tissue during pars plana vitrectomy with or without membrane removal. An independent masked observer will evaluate the primary efficacy. Approximately 66 patients to obtain 60 evaluable patients will be enrolled.

Primary efficacy consisted of the evaluation of the visualization of posterior segment structures in pars plana vitrectomy before and after instillation of triamcinolone acetonide. The assessment was based upon a masked review of videos images taken before and after use of triamcinolone acetonide. Secondary efficacy was determined by the surgeon's assessment of triamcinolone acetonide's ability to improve visualization. This assessment was based on judgment of how visualization compares prior to and following instillation of the study medication.

Safety variables include intraocular pressure, slit-lamp assessment of anterior segment inflammation (aqueous cells, aqueous flare, and corneal edema), and dilated fundus assessment of vitreous haze, retina, macula, choroid and optic nerve. Patients will be examined preoperatively, in addition to Days 1 and 7 following surgery.

**Schedule of Exams:**

| Study Activity | Activities to be Performed by Study Visit | | | |
|---|---|---|---|---|
| | **Preop. Baseline** | **Surgery** | **Post-operative** | |
| | **4 Weeks to Day 0** | **Day 0** | **Day 1** | **Day 7 (±2 days) / Exit** |
| Informed consent | X | | | |
| Urine pregnancy test | $X_A$ | | | |
| Demographics | X | | | |
| General information: Medical history (systemic/ocular conditions and prior surgeries) | X | X | | |
| Concomitant medications (non-surgical) | X | X | X | X |
| Intraocular pressure | $X_B$ | | $X_S$ | $X_B$ |
| Slit-lamp examination: ocular inflammation (cells, flare, corneal edema) | $X_B$ | | $X_B$ | $X_B$ |
| Dilated fundus examination (vitreous haze, retina, macula, choroid, optic nerve) | $X_B$ | $X_{S,\dagger}$ | $X_B$ | $X_B$ |
| Anterior segment assessment | | $X_{B,\dagger}$ | | |
| Instill study medication for visualization of vitreous (and for membranes, as necessary) | | $X_S$ | | |
| Collection of vitreous images | | $X_S$ | | |
| Surgeon questionnaire regarding visualization | | X | | |
| Surgically-related medications | | X | X | X |
| Surgically-related ocular conditions | | | $X_S$ | $X_S$ |
| Record adverse events | | X | X | X |
| Complete Exit Form | | | | X |

[A] Female patients of childbearing potential, [B] Both eyes, [S] Study eye only, [†] Prior to surgery and administration of test article

**Patient population**

| **Safety Population** **N=** | **Intent –to-Treat (ITT)/Safety** **N=** | **Per Protocol (PP)** **N=** |
|---|---|---|
| 60 eyes | 60 eyes | 58 eyes |

**Reviewer's Comments:**

*Sixty eyes were enrolled (ITT population) and 58 eyes were in the Per Protocol Analysis (PP); two eyes were not evaluable due to significant protocol deviations - 1 eye had had a previous vitrectomy and the other had a previous vitrectomy with silicone oil in the study eye.*

### 6.1.4 Efficacy Findings:

Sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory unresponsive to topical corticosteroids

There is over a 40 year history of use of the active ingredient, triamcinolone acetonide, in the United States (marketed by Bristol-Myers, Squibb, Princeton, NJ, as KENALOG-40) with adequate demonstration of safety and efficacy for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory unresponsive to topical corticosteroids. These ophthalmic indications are supported by the Agency's previous findings of safety and effectiveness for NDA 14-901 (Kenalog-40, 505(b)(2) indications).

The applicant's literature search supports the approval for theses 505(b)(2) indications. Disease entities such as sympathetic ophthalmia and temporal arteritis are rare and the literature is limited to small case series evaluations. Many case studies report favorable visual acuity outcomes following treatment with triamcinolone acetonide in patients diagnosed with uveitis or posterior segment inflammation. For these indications, in general, triamcinolone acetonide by periocular or intravitreal route at doses from 2 to 40 mg demonstrated a favorable effect on visual acuity outcomes.

**Reviewer's outcomes:**

*The results from the applicant's review of the literature for the 505(b)(2) indications of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory unresponsive to topical corticosteroids are consistent with the Agency's previous findings of safety and effectiveness for Kenalog-40, triamcinolone acetonide.*

*Study C-06-26 demonstrates the benefit of triamcinolone acetonide for sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory unresponsive to topical corticosteroids.*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Visualization of the vitreous during vitrectomy

**Table 13 – Percentage of Eyes in which TA was Declared Useful for Visualization**
**Study C-06-26**
**A meta-analysis**

| | | | TA was safe and effective for visualization | |
|---|---|---|---|---|
| | **Articles** | **Total N** | **N** | **%** |
| **All Reported Techniques Combined** | 33 | 3051 | 3040 | 99.6 |
| **Membrane(s)** | | | | |
| **Vitrectomy** | 19 | 2462 | 2461 | 100 |
| **Vitrectomy** | 8 | 2199 | 2198 | 100 |

**Table 14 – Mean Visualization Score (ITT)**
**Study C-05-62**
**(Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)**

| | **Mean** | **Std** | **N** | **P-value*** |
|---|---|---|---|---|
| **Pre-instillation** | 0.5 | 0.6 | 60 | |
| **Post-instillation** | 3.7 | 0.8 | 60 | |
| **Change** | 3.2 | 0.9 | 60 | 0.0001 |

* A paired t-test comparing visualization scores of posterior segment structures before and after instillation of TA.

**Table 15 – Degree of Visualization (ITT)**
**Study C-05-62**
**(Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)**

| | **Not Visible "0"** | | **"1"** | | **"2"** | | **"3"** | | **Clearly Delineated "4"** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Pre-instillation** | 36 | 60.0 | 20 | 33.3 | 4 | 6.7 | 0 | 0 | 0 | 0 |
| **Post-instillation** | 1 | 1.7 | 2 | 3.3 | 2 | 3.3 | 5 | 8.3 | 50 | 83.3 |

**Reviewer's comments:**

*For tables 14 and 15 the ITT results are similar to the PP results (PP results not shown).*

*For Clinical trial C-05-62 the p-value was statistically significant at p<0.0001.*

*Study C-06-2, combined with the results from Study Clinical trial C-05-62, demonstrates the benefit of TA for visualization during a vitrectomy.*

### 6.1.5 Clinical Microbiology

There is no Clinical Microbiology review for this product. It is not an anti-infective.

### 6.1.6 Efficacy Conclusions

The application supports the effectiveness of triamcinolone acetonide for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and the visualization of the vitreous during vitrectomy.

The major sources of clinical data in support of efficacy for triamcinolone acetonide utilized in this review include:

- Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report)
- Data from the Clinical trial C-05-62: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery.

# 7 INTEGRATED REVIEW OF SAFETY

## 7.1 Methods and Findings

The submitted study report for the meta-analysis C-06-26 and data from the clinical trial C-05-62 were reviewed. The submitted study reports form the basis of the review of safety for this application.

The total dataset for safety evaluation consisted of 18,653 eyes and 13,983 patients receiving any treatment in Study C-06-26 plus an additional 60 eyes were enrolled into the safety data base from clinical study C-05-62.

In study C-06-26, intravitreal triamcinolone acetonide therapy was evaluated in 14,291 eyes and 10,083 patients as either primary or adjunctive therapy. The proposed target dose of

triamcinolone acetonide in this application is 4 mg administered by intravitreal injection. One hundred, forty-six articles with 4081 eyes and 4119 patients evaluated intravitreal triamcinolone acetonide 4 mg as primary therapy and 30 article with 616 eyes and 563 patients evaluated intravitreal triamcinolone acetonide 4 mg administered with adjunctive therapy (PDT, TTT, other photocoagulation, and other therapies). Doses of intravitreal triamcinolone acetonide other than 4 mg were categorized as up to 4 mg (e.g. less than 4mg), 5 to <20 mg, and > 20 mg and analyzed to determine if there were any dose-related safety issues.

Periocular dosing of triamcinolone acetonide was evaluated in 1286 eyes and 1178 patients. Analyses of periocular dosing of triamcinolone acetonide (including subtenon, posterior juxtascleral depot, retrobulbar, and subconjunctival) were compared to intravitreal dosing to assess differences in the safety between routes of administration.

The dosing ranges proposed for periocular therapy were identical to those defined for intravitreal administration. However, there were no articles which evaluated periocular triamcinolone acetonide 4 mg. The remaining periocular dosing categories included less than 4 mg triamcinolone acetonide, 5 to <20 mg triamcinolone acetonide, and >20 mg triamcinolone acetonide.

Control therapies evaluated included untreated controls (1171 eyes and 1115 patients), eyes receiving PDT (574 eyes and 574 patients), other forms of photocoagulation (including TTT and photocoagulation NOS) (306 eyes and 270 patients), and eyes treated with vehicle/sham/placebo periocular injections (411 eyes and 153 patients). There were no articles which evaluated intravitreal administration of placebo/vehicle/sham. Therefore, the primary comparative analysis is to untreated control eyes.

For clinical study C-05-62 60 eyes were enrolled where 1 – 4 mg of triamcinolone acetonide was administered as needed for visualization during pars plana vitrectomy with or without membrane removal.

### 7.1.1 Deaths

In study C-06-26 there were 2 deaths reported, 1 in the intravitreal triamcinolone acetonide 4 mg primary therapy group and 1 in the periocular ≥ 20 mg triamcinolone acetonide adjunctive therapy group. In both cases, there was no information provided in the article to assess the reason for death or the relationship to study treatment.

In study C-05-62 no deaths were reported.

### 7.1.2 Other Serious Adverse Events

**Table 7.1.2 A - Study C-06-26**
**Frequency of adverse events by treatment**
**Intravitreal route**

| | | All Intravitreal Treatments | | 4 mg Triamcinolone Primary Therapy | | 4 mg Triamcinolone + Adjunctive Therapy | | Less than 4 mg Triamcinolone Primary Therapy | | Less than 4 mg Triamcinolone + Adjunctive Therapy | | 5-<20 mg Triamcinolone Primary Therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SOC | Coded Event | N | % | N | % | N | % | N | % | N | % | N | % |
| Patients in Treatment Group | | 11265 | 100.0 | 3373 | 100.0 | 485 | 100.0 | 1089 | 100.0 | 20 | 100.0 | 2763 | 100.0 |
| Infections and infestations | Hypopyon | 17 | 0.2 | 13 | 0.4 | . | . | 1 | 0.1 | . | . | 2 | 0.1 |
| Eye disorders | Endophthalmitis | 63 | 0.6 | 42 | 1.2 | . | . | 16 | 1.5 | . | . | 3 | 0.1 |
| | Retinal detachment | 31 | 0.3 | 11 | 0.3 | 4 | 0.8 | . | . | . | . | 3 | 0.1 |
| | Vitreous haemorrhage | 26 | 0.2 | 9 | 0.3 | . | . | 2 | 0.2 | . | . | 11 | 0.4 |
| | Glaucoma | 13 | 0.1 | 6 | 0.2 | . | . | 1 | 0.1 | . | . | 1 | <0.1 |
| | Visual acuity reduced | 6 | 0.1 | 5 | 0.1 | . | . | . | . | . | . | 1 | <0.1 |
| | Retinal haemorrhage | 6 | 0.1 | 4 | 0.1 | 2 | 0.4 | . | . | . | . | . | . |
| | Conjunctival haemorrhage | 7 | 0.1 | 4 | 0.1 | . | . | 3 | 0.3 | . | . | . | . |
| | Maculopathy | 9 | 0.1 | 4 | 0.1 | . | . | 2 | 0.2 | 3 | 15.0 | . | . |
| | Vitreous detachment | 4 | <0.1 | 3 | 0.1 | . | . | 1 | 0.1 | . | . | . | . |
| | Vitreous floaters | 15 | 0.1* | 3 | 0.1* | . | . | . | . | .* | . | 12 | 0.4 |
| | Ocular discomfort | 3 | <0.1* | 3 | 0.1* | . | . | . | . | . | . | . | . |
| | Optic disc haemorrhage | 3 | <0.1 | 3 | 0.1 | . | . | . | . | . | . | . | . |
| | Retinal vein occlusion | 3 | <0.1 | 2 | 0.1 | . | . | . | . | . | . | . | . |
| | Optic ischaemic neuropathy | 2 | <0.1 | 2 | 0.1 | . | . | . | . | . | . | . | . |
| | Iris neovascularisation | 1 | <0.1 | 1 | <0.1 | . | . | . | . | . | . | . | . |
| | Macular hole | 1 | <0.1 | 1 | <0.1 | . | . | . | . | . | . | . | . |
| | Retinal exudates | 1 | <0.1 | 1 | <0.1 | . | . | . | . | . | . | . | . |
| | Detachment of retinal pigment epithelium | 10 | 0.1 | . | . | 4 | 0.8 | . | . | . | . | . | . |
| | Optic disc vascular disorder | 10 | 0.1 | . | . | . | . | 10 | 0.9 | . | . | . | . |
| | Eye inflammation | 8 | 0.1 | . | . | . | . | 8 | 0.7 | . | . | . | . |

**Table 7.1.2 A - Study C-06-26**
**Frequency of adverse events by treatment (continued)**
**Intravitreal route**

Route: Intravitreal

| | | 5-<20 mg Triamcinolone + Adjunctive Therapy | | ≥ 20 mg Triamcinolone Primary Therapy | | ≥ 20 mg Triamcinolone + Adjunctive Therapy | | Missing | |
|---|---|---|---|---|---|---|---|---|---|
| SOC | Coded Event | N | % | N | % | N | % | N | % |
| Patients in Treatment Group | | 71 | 100.0 | 1936 | 100.0 | 1259 | 100.0 | 269 | 100.0 |
| Infections and infestations | Hypopyon | . | . | 1 | 0.1 | . | . | . | . |
| Eye disorders | Endophthalmitis | . | . | 1 | 0.1 | 1 | 0.1 | . | . |
| | Retinal detachment | . | . | 9 | 0.5 | 2 | 0.2 | 2 | 0.7 |
| | Vitreous haemorrhage | . | . | 3 | 0.2 | . | . | 1 | 0.4 |
| | Glaucoma | 4 | 5.6 | . | . | . | . | 1 | 0.4 |
| | Visual acuity reduced | . | . | . | . | . | . | . | . |
| | Retinal haemorrhage | . | . | . | . | . | . | . | . |
| | Conjunctival haemorrhage | . | . | . | . | . | . | . | . |
| | Maculopathy | . | . | . | . | . | . | . | . |
| | Vitreous detachment | . | . | . | . | . | . | . | . |
| | Vitreous floaters | . | . | . | . | . | . | . | . |
| | Ocular discomfort | . | . | . | . | . | . | . | . |
| | Optic disc haemorrhage | . | . | . | . | . | . | . | . |
| | Retinal vein occlusion | 1 | 1.4 | . | . | . | . | . | . |
| | Optic ischaemic neuropathy | . | . | . | . | . | . | . | . |
| | Iris neovascularisation | . | . | . | . | . | . | . | . |
| | Macular hole | . | . | . | . | . | . | . | . |
| | Retinal exudates | . | . | . | . | . | . | . | . |
| | Detachment of retinal pigment epithelium | . | . | . | . | 6 | 0.5 | . | . |
| | Optic disc vascular disorder | . | . | . | . | . | . | . | . |
| | Eye inflammation | . | . | . | . | . | . | . | . |

**Table 7.1.2 A - Study C-06-26**
**Frequency of adverse events by treatment (continued)**
**Intravitreal route**

| | | All Intravitreal Treatments | | 4 mg Triamcinolone Primary Therapy | | 4 mg Triamcinolone + Adjunctive Therapy | | Less than 4 mg Triamcinolone Primary Therapy | | Less than 4 mg Triamcinolone + Adjunctive Therapy | | 5-<20 mg Triamcinolone Primary Therapy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SOC | Coded Event | N | % | N | % | N | % | N | % | N | % | N | % |
| Patients in Treatment Group | | 11265 | 100.0 | 3373 | 100.0 | 485 | 100.0 | 1089 | 100.0 | 20 | 100.0 | 2763 | 100.0 |
| | Anterior chamber inflammation | 5 | <0.1 | . | . | . | . | 4 | 0.4 | . | . | 1 | <0.1 |
| | Retinal tear | 39 | 0.3 | . | . | . | . | . | . | . | . | 34 | 1.2 |
| | Posterior capsule rupture | 25 | 0.2 | . | . | . | . | . | . | . | . | 24 | 0.9 |
| | Anterior chamber fibrin | 3 | <0.1 | . | . | . | . | . | . | . | . | 3 | 0.1 |
| | Corneal epithelium defect | 2 | <0.1 | . | . | . | . | . | . | . | . | 1 | <0.1 |
| | Vitritis | 1 | <0.1 | . | . | . | . | . | . | . | . | 1 | <0.1 |
| | Subretinal fibrosis | 2 | <0.1 | . | . | . | . | . | . | . | . | . | . |
| | Vitreous prolapse | 3 | <0.1 | . | . | . | . | . | . | . | . | . | . |
| | Retinal pigment epitheliopathy | 2 | <0.1 | . | . | . | . | . | . | . | . | . | . |
| General disorders and administration site conditions | Injection site reaction | 34 | 0.3 | 5 | 0.1 | . | . | . | . | . | . | 29 | 1.0 |
| | Death | 1 | <0.1 | 1 | <0.1 | . | . | . | . | . | . | . | . |
| Injury, poisoning and procedural complications | Post procedural haemorrhage | 5 | <0.1 | 5 | 0.1 | . | . | . | . | . | . | . | . |
| | Intraocular lens dislocation | 1 | <0.1 | . | . | . | . | . | . | . | . | . | . |

**Table 7.1.2 A Study C-06-26**
**Frequency of adverse events by treatment (continued)**
**Intravitreal route**

| | | 5-<20 mg Triamcinolone + Adjunctive Therapy | | ≥ 20 mg Triamcinolone Primary Therapy | | ≥ 20 mg Triamcinolone + Adjunctive Therapy | | Missing | |
|---|---|---|---|---|---|---|---|---|---|
| SOC | Coded Event | N | % | N | % | N | % | N | % |
| Patients in Treatment Group | | 71 | 100.0 | 1936 | 100.0 | 1259 | 100.0 | 269 | 100.0 |
| | Anterior chamber inflammation | . | . | . | . | . | . | . | . |
| | Retinal tear | . | . | . | . | . | . | 5 | 1.9 |
| | Posterior capsule rupture | . | . | 1 | 0.1 | . | . | . | . |
| | Anterior chamber fibrin | . | . | . | . | . | . | . | . |
| | Corneal epithelium defect | . | . | . | . | . | . | 1 | 0.4 |
| | Vitritis | . | . | . | . | . | . | . | . |
| | Subretinal fibrosis | 2 | 2.8 | . | . | . | . | . | . |
| | Vitreous prolapse | . | . | 3 | 0.2 | . | . | . | . |
| | Retinal pigment epitheliopathy | . | . | . | . | 2 | 0.2 | . | . |
| General disorders and administration site conditions | Injection site reaction | . | . | . | . | . | . | . | . |
| | Death | . | . | . | . | . | . | . | . |
| Injury, poisoning and procedural complications | Post procedural haemorrhage | . | . | . | . | . | . | . | . |
| | Intraocular lens dislocation | . | . | 1 | 0.1 | . | . | . | . |

* Overall incidence of these events may be higher than reported since some authors commented that these events occurred during the study, but did not indicate the number of eyes affected.
N=number of patients
5 articles (Avitabile et al. 2005, Kreissig et al. 2006, Nkeme et al. 2006, Sakamoto et al. 2004, Westfall et al. 2005) indicated only the number of eyes in the study and not the number of patients
SOC=System Organ Class

**Reviewer's comments:**

*Intravitreal administration:*

*The most frequently reported adverse events with any dose of intravitreal triamcinolone acetonide were endophthalmitis (0.6%), retinal detachment (0.3%), retinal tear (0.3%), injection site reactions (0.3%), posterior capsule rupture (0.2%) and vitreous hemorrhage (0.2%). All other events occurred at an incidence of 0.1% or less. Adverse events commonly reported with intravitreal triamcinolone acetonide 4 mg primary therapy included endophthalmitis (1.2%), hypopyon (0.4%), retinal detachment (0.3%), vitreous hemorrhage (0.3%) and glaucoma (0.2%).*

*The use of intravitreal triamcinolone acetonide does not present an unacceptable safety risk to patients based upon a comprehensive review of the literature. Common observations following treatment, including increased intraocular pressure and cataract progression, can be managed within a clinical setting. The risk of infectious endophthalmitis is low and comparable to that reported with other intravitreal therapies.*

**Table 7.1.2 B - Study C-06-26**
**Frequency of adverse events by treatment**
**Periocular route**

| | | All Periocular Treatments | | Less than 4 mg Triamcinolone Primary Therapy | | 5-<20 mg Triamcinolone Primary Therapy | | ≥ 20 mg Triamcinolone Primary Therapy | | ≥ 20 mg Triamcinolone + Adjunctive Therapy | | Placebo Vehicle Sham | | Missing | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SOC | Coded Event | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Patients in Treatment Group | | 810 | 100.0 | 35 | 100.0 | 37 | 100.0 | 497 | 100.0 | 115 | 100.0 | 125 | 100.0 | 1 | 100.0 |
| Nervous system disorders | Headache | 8 | 1.0 | . | . | . | . | 8 | 1.6 | . | . | . | . | . | . |
| | Cerebrovascular accident | 1 | 0.1 | . | . | . | . | 1 | 0.2 | . | . | . | . | . | . |
| Eye disorders | Conjunctival haemorrhage | 8 | 1.0* | 5 | 14.3 | . | . | 3 | 0.6* | . | . | . | . | . | . |
| | Eyelid ptosis | 10 | 1.2* | . | . | . | . | 8 | 1.6* | 2 | 1.7 | . | . | . | . |
| | Glaucoma | 7 | 0.9 | . | . | . | . | 7 | 1.4 | . | . | . | . | . | . |
| | Conjunctival oedema | 2 | 0.2* | . | . | . | . | 2 | 0.4* | . | . | . | . | . | . |
| | Anterior chamber inflammation | 1 | 0.1 | . | . | . | . | 1 | 0.2 | . | . | . | . | . | . |
| | Choroiditis | 1 | 0.1 | . | . | . | . | 1 | 0.2 | . | . | . | . | . | . |
| | Retinal haemorrhage | 1 | 0.1 | . | . | . | . | 1 | 0.2 | . | . | . | . | . | . |
| | Maculopathy | 2 | 0.2 | . | . | . | . | . | . | 2 | 1.7 | . | . | . | . |
| | Conjunctivitis | 1 | 0.1 | . | . | . | . | . | . | 1 | 0.9 | . | . | . | . |
| | Macular oedema | 1 | 0.1 | . | . | . | . | . | . | 1 | 0.9 | . | . | . | . |
| | Vitreous haemorrhage | 3 | 0.4 | . | . | . | . | . | . | . | . | 3 | 2.4 | . | . |
| | Corneal decompensation | 1 | 0.1 | . | . | . | . | . | . | . | . | 1 | 0.8 | . | . |
| Skin and subcutaneous tissue disorders | Ecchymosis | 3 | 0.4 | . | . | . | . | 3 | 0.6 | . | . | . | . | . | . |
| | Hirsutism | 1 | 0.1 | . | . | . | . | 1 | 0.2 | . | . | . | . | . | . |
| General disorders and administration site conditions | Death | 1 | 0.1 | . | . | . | . | . | . | 1 | 0.9 | . | . | . | . |
| Injury, poisoning and procedural complications | Procedural pain | 31 | 3.8 | . | . | . | . | 31 | 6.2 | . | . | . | . | . | . |

* Overall incidence of these events may be higher than reported since some authors commented that these events occurred during the study, but did not indicate the number of eyes affected.

N=number of patients SOC=System Organ Class

5 articles (Avitabile et al. 2005, Kreissig 2006, Nkeme et al. 2006, Sakamoto et al. 2004, Westfall et al. 2005) indicated only the number of eyes in the study and not the number of patients.

**Reviewer's Comments:**

*Periocular Administration:*

*The most frequently reported adverse events with any dose of periocular triamcinolone acetonide included procedural pain (3.8%), eyelid ptosis (1.2%), headache (1.0%), conjunctival hemorrhage (1.0 %), and glaucoma (0.9%). The incidence of adverse events reported for glaucoma was slightly higher with periocular administration than with intravitreal administration. Whether this is related to a different effect of route of administration, the higher doses used within the periocular studies or difference in the number of eyes treated between treatment routes is unknown.*

*Overall, adverse events reported with periocular triamcinolone acetonide were similar to those reported with intravitreal administration, except for eyelid ptosis and headache which were more common with periocular administration.*

### 7.1.3 Dropouts and Other Significant Adverse Events

For Study C-06-26 there is no dropout profile information provided for the cited literature references describing other clinical trials. For complications related to increased IOP or cataract progression the data was not captured in the adverse event/complication section, but summarized within the IOP and cataract panels of the CRF.

For study C-05-62 there were no deaths, other serious adverse events, or other significant adverse events reported during the study.

**Table 7.1.3 B – Study C-06-26**
**Maximum frequency and incidence of Elevated Intraocular pressure (mmHg) at any of Follow-up Visit and by Treatment**
**Intravitreal route**

| | | Number with Elevated IOP | Number Treated for Elevated IOP | Number Controlled with Topical Meds | Number Controlled by Surgical or Non-Topical Treatment | Number Not Controlled by Any Treatment |
|---|---|---|---|---|---|---|
| All Intravitreal Treatments | No. Observed | 2293 | 1723 | 1640 | 74 | 2 |
| | % | 32.0 | 29.9 | 28.8 | 2.2 | 0.1 |
| | No. of Eyes | 7162 | 5757 | 5700 | 3414 | 1659 |
| | No. of Articles | 203 | 182 | 178 | 92 | 58 |
| Less than 4 mg Triamcinolone Primary Therapy | No. Observed | 129 | 89 | 84 | 5 | 0 |
| | % | 26.8 | 20.4 | 19.2 | 1.4 | 0.0 |
| | No. of Eyes | 482 | 437 | 437 | 358 | 76 |
| | No. of Articles | 12 | 11 | 11 | 7 | 3 |
| Less than 4 mg Triamcinolone + Adjunctive Therapy | No. Observed | 20 | 20 | 19 | 1 | . |
| | % | 58.8 | 58.8 | 55.9 | 8.3 | . |
| | No. of Eyes | 34 | 34 | 34 | 12 | . |
| | No. of Articles | 2 | 2 | 2 | 1 | . |
| 4 mg Triamcinolone Primary Therapy | No. Observed | 1029 | 642 | 605 | 42 | 2 |
| | % | 34.2 | 31.0 | 29.6 | 3.7 | 0.4 |
| | No. of Eyes | 3012 | 2071 | 2045 | 1137 | 494 |
| | No. of Articles | 109 | 98 | 95 | 51 | 32 |
| 4 mg Triamcinolone + Adjunctive Therapy | No. Observed | 115 | 112 | 111 | 1 | 0 |
| | % | 25.6 | 24.9 | 24.7 | 0.9 | 0.0 |
| | No. of Eyes | 449 | 449 | 449 | 115 | 67 |
| | No. of Articles | 22 | 22 | 22 | 6 | 5 |

**Table 7.1.3 B – Study C-06-26**
**Maximum frequency and incidence of Elevated Intraocular pressure (mmHg) at any of Follow-up Visit and by Treatment (continued)**
**Intravitreal route**

| | | Number with Elevated IOP | Number Treated for Elevated IOP | Number Controlled with Topical Meds | Number Controlled by Surgical or Non-Topical Treatment | Number Not Controlled by Any Treatment |
|---|---|---|---|---|---|---|
| 5-<20 mg Triamcinolone Primary Therapy | No. Observed | 241 | 230 | 222 | 8 | 0 |
| | % | 21.2 | 21.2 | 20.5 | 2.0 | 0.0 |
| | No. of Eyes | 1136 | 1085 | 1085 | 406 | 312 |
| | No. of Articles | 17 | 15 | 15 | 7 | 6 |
| 5-<20 mg Triamcinolone + Adjunctive Therapy | No. Observed | 30 | 30 | 29 | 1 | 0 |
| | % | 43.5 | 43.5 | 42.0 | 1.8 | 0.0 |
| | No. of Eyes | 69 | 69 | 69 | 55 | 41 |
| | No. of Articles | 4 | 4 | 4 | 3 | 2 |
| ≥ 20 mg Triamcinolone Primary Therapy | No. Observed | 673 | 544 | 518 | 12 | 0 |
| | % | 38.8 | 39.8 | 38.8 | 1.1 | 0.0 |
| | No. of Eyes | 1734 | 1366 | 1335 | 1096 | 659 |
| | No. of Articles | 33 | 26 | 25 | 14 | 9 |
| ≥ 20 mg Triamcinolone + Adjunctive Therapy | No. Observed | 56 | 56 | 52 | 4 | 0 |
| | % | 22.8 | 22.8 | 21.1 | 1.7 | 0.0 |
| | No. of Eyes | 246 | 246 | 246 | 235 | 10 |
| | No. of Articles | 4 | 4 | 4 | 3 | 1 |

No Observed=number of eyes
6 articles (Bui et al. 2002, Jonas et al. 2002, Jonas et al. 2003b, Konjevic et al. 2006, Opremcak et al. 2006, Lee SY et al. 2006) indicated only the number of patients and not number of eyes.

**Table 7.1.3 C – Study C-06-26**
**Maximum frequency and incidence of Elevated Intraocular pressure (mmHg) at any of Follow-up Visit and by Treatment**
**Periocular route**

| | | Number with Elevated IOP | Number Treated for Elevated IOP | Number Controlled with Topical Meds | Number Controlled by Surgical or Non-Topical Treatment | Number Not Controlled by Any Treatment |
|---|---|---|---|---|---|---|
| All Periocular Treatments | No. Observed | 212 | 184 | 140 | 32 | 0 |
| | % | 16.1 | 15.8 | 12.6 | 4.5 | 0.0 |
| | No. of Eyes | 1313 | 1166 | 1113 | 715 | 391 |
| | No. of Articles | 41 | 36 | 35 | 21 | 12 |
| Less than 4 mg Triamcinolone Primary Therapy | No. Observed | 6 | 6 | 4 | 2 | . |
| | % | 15.8 | 15.8 | 10.5 | 5.3 | . |
| | No. of Eyes | 38 | 38 | 38 | 38 | . |
| | No. of Articles | 1 | 1 | 1 | 1 | . |
| 5-<20 mg Triamcinolone Primary Therapy | No. Observed | 5 | 1 | 1 | . | . |
| | % | 7.8 | 2.9 | 2.9 | . | . |
| | No. of Eyes | 64 | 35 | 35 | . | . |
| | No. of Articles | 2 | 1 | 1 | . | . |
| 5-<20 mg Triamcinolone + Adjunctive Therapy | No. Observed | 0 | 0 | 0 | 0 | 0 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | No. of Eyes | 10 | 10 | 10 | 10 | 10 |
| | No. of Articles | 1 | 1 | 1 | 1 | 1 |
| ≥ 20 mg Triamcinolone Primary Therapy | No. Observed | 173 | 164 | 126 | 26 | 0 |
| | % | 19.0 | 19.1 | 15.7 | 4.6 | 0.0 |
| | No. of Eyes | 910 | 858 | 805 | 563 | 297 |
| | No. of Articles | 27 | 25 | 24 | 14 | 7 |

**Table 7.1.3 C – Study C-06-26**
**Maximum frequency and incidence of Elevated Intraocular pressure (mmHg) at any of Follow-up Visit and by Treatment (continued)**
**Periocular route**

| | | Number with Elevated IOP | Number Treated for Elevated IOP | Number Controlled with Topical Meds | Number Controlled by Surgical or Non-Topical Treatment | Number Not Controlled by Any Treatment |
|---|---|---|---|---|---|---|
| ≥ 20 mg Triamcinolone + Adjunctive Therapy | No. Observed | 12 | 11 | 7 | 4 | 0 |
| | % | 10.1 | 9.2 | 5.9 | 3.8 | 0.0 |
| | No. of Eyes | 119 | 119 | 119 | 104 | 84 |
| | No. of Articles | 6 | 6 | 6 | 5 | 4 |
| Placebo/Vehicle/Sham | No. Observed | 16 | 2 | 2 | . | . |
| | % | 9.3 | 1.9 | 1.9 | . | . |
| | No. of Eyes | 172 | 106 | 106 | . | . |
| | No. of Articles | 4 | 2 | 2 | . | . |

No Observed=number of eyes
6 articles (Bui et al. 2002, Jonas et al. 2002, Jonas et al. 2003b, Konjevic et al. 2006, Opremcak et al. 2006, Lee SY et al. 2006) indicated only the number of patients and not number of eyes.

**Reviewer's comments:**

*The overall incidence of eyes with elevated IOP with intravitreal triamcinolone acetonide at any follow-up visit was 32.0% (ranging from 25.6-58.8% across all treatment regimens). Approximately 30% of eyes required treatment for elevation in IOP, including 28.7% requiring topical treatment and 2.2% requiring more aggressive therapies (filtration surgery, surgical removal of the triamcinolone acetonide depot, etc.). Similar percentages were reported for eyes receiving intravitreal triamcinolone acetonide 4 mg. Two eyes, both receiving triamcinolone acetonide 4mg intravitreal as primary therapy failed to achieve documented control of IOP. One eye received multiple injections and the other eye 1 single injection. In both instances the elevation in IOP was treated with topical ocular medication only and eyes had persistent elevations in IOP. No mention of either eye undergoing surgical treatment was documented.*

*Periocular administration of triamcinolone acetonide appeared to be associated with a lower incidence of elevations in IOP, 16.1% (range 7.8% to 19.0%). Whether this is due to less effect of periocular administration on IOP or the result of the smaller number of eyes evaluated with periocular dosing is uncertain. Even though periocular dosing of triamcinolone acetonide may be associated with a slightly lower incidence of IOP elevation, the overall incidence of eyes requiring surgical or nontopical treatment for IOP was similar among intravitreal and periocular routes (2.2% for intravitreal, 4.5% for periocular).*

**Table 7.1.3 D – Study C-06-26**
**Overall Frequency and Incidence of cataract progression**
**Intravitreal route**

| | | Cortical | Posterior Subcapsular | Nuclear | Total |
|---|---|---|---|---|---|
| **All Intravitreal Treatments** | **No. Observed** | 6 | 102 | 13 | 289 |
| | **%** | 1.2 | 8.9 | 2.1 | 12.0 |
| | **No. of Eyes** | 530 | 1150 | 622 | 2406 |
| | **No. of Articles** | 37 | 63 | 41 | 103 |
| **Less than 4 mg Triamcinolone Primary Therapy** | **No. Observed** | 0 | 0 | 0 | 8 |
| | **%** | 0.0 | 0.0 | 0.0 | 2.8 |
| | **No. of Eyes** | 53 | 53 | 53 | 281 |
| | **No. of Articles** | 3 | 3 | 3 | 5 |
| **Less than 4 mg Triamcinolone + Adjunctive Therapy** | **No. Observed** | . | . | . | 2 |
| | **%** | . | . | . | 5.9 |
| | **No. of Eyes** | . | . | . | 34 |
| | **No. of Articles** | . | . | . | 2 |
| **4 mg Triamcinolone Primary Therapy** | **No. Observed** | 4 | 78 | 9 | 161 |
| | **%** | 1.3 | 9.3 | 2.3 | 14.4 |
| | **No. of Eyes** | 316 | 838 | 397 | 1116 |
| | **No. of Articles** | 24 | 46 | 27 | 65 |
| **4 mg Triamcinolone + Adjunctive Therapy** | **No. Observed** | 2 | 14 | 3 | 40 |
| | **%** | 2.0 | 7.9 | 3.0 | 13.6 |
| | **No. of Eyes** | 100 | 177 | 100 | 294 |
| | **No. of Articles** | 5 | 7 | 5 | 12 |
| **5-<20 mg Triamcinolone Primary Therapy** | **No. Observed** | 0 | 10 | 0 | 35 |
| | **%** | 0.0 | 25.0 | 0.0 | 10.2 |
| | **No. of Eyes** | 19 | 40 | 19 | 344 |
| | **No. of Articles** | 2 | 4 | 2 | 8 |

**Table 7.1.3 D – Study C-06-26**
**Overall Frequency and Incidence of cataract progression (continued)**
**Intravitreal route**

| | | Cortical | Posterior Subcapsular | Nuclear | Total |
|---|---|---|---|---|---|
| 5-<20 mg Triamcinolone + Adjunctive Therapy | No. Observed | . | . | . | 16 |
| | % | . | . | . | 32.0 |
| | No. of Eyes | . | . | . | 50 |
| | No. of Articles | . | . | . | 3 |
| ≥ 20 mg Triamcinolone Primary Therapy | No. Observed | 0 | 0 | 0 | 26 |
| | % | 0.0 | 0.0 | 0.0 | 9.4 |
| | No. of Eyes | 42 | 42 | 42 | 276 |
| | No. of Articles | 3 | 3 | 3 | 7 |
| ≥ 20 mg Triamcinolone + Adjunctive Therapy | No. Observed | . | . | 1 | 1 |
| | % | . | . | 9.1 | 9.1 |
| | No. of Eyes | . | . | 11 | 11 |
| | No. of Articles | . | . | 1 | 1 |

No Observed=number of eyes
1 article (Opremcak et al. 2006) indicated only the number of patients and not number of eyes.

**Table 7.1.3 F – Study C-05-62**
**Overall Frequency and Incidence of cataract progression**
**Periocular route**

| | | Cortical | Posterior Subcapsular | Nuclear | Total |
|---|---|---|---|---|---|
| **All Periocular Treatments** | **No. Observed** | 3 | 8 | 2 | 56 |
| | **%** | 1.0 | 2.1 | 0.7 | 10.1 |
| | **No. of Eyes** | 307 | 377 | 307 | 556 |
| | **No. of Articles** | 12 | 14 | 12 | 20 |
| **Less than 4 mg Triamcinolone Primary Therapy** | **No. Observed** | . | . | . | 2 |
| | **%** | . | . | . | 5.3 |
| | **No. of Eyes** | . | . | . | 38 |
| | **No. of Articles** | . | . | . | 1 |
| **5-<20 mg Triamcinolone Primary Therapy** | **No. Observed** | 0 | 0 | 0 | 0 |
| | **%** | 0.0 | 0.0 | 0.0 | 0.0 |
| | **No. of Eyes** | 29 | 29 | 29 | 29 |
| | **No. of Articles** | 1 | 1 | 1 | 1 |
| **≥ 20 mg Triamcinolone Primary Therapy** | **No. Observed** | 0 | 7 | 0 | 50 |
| | **%** | 0.0 | 2.3 | 0.0 | 10.5 |
| | **No. of Eyes** | 238 | 308 | 238 | 478 |
| | **No. of Articles** | 9 | 11 | 9 | 16 |
| **≥ 20 mg Triamcinolone + Adjunctive Therapy** | **No. Observed** | 0 | 0 | 0 | 4 |
| | **%** | . | . | . | 36.4 |
| | **No. of Eyes** | 0 | 0 | 0 | 11 |
| | **No. of Articles** | 1 | 1 | 1 | 2 |
| **Placebo/Vehicle/Sham** | **No. Observed** | 3 | 1 | 2 | . |
| | **%** | 7.5 | 2.5 | 5.0 | . |
| | **No. of Eyes** | 40 | 40 | 40 | . |
| | **No. of Articles** | 1 | 1 | 1 | . |

No Observed=number of eyes
1 article (Opremcak et al. 2006) indicated only the number of patients and not number of eyes.

**Reviewer's comments:**

*Cataract progression was described in 114 articles with intravitreal triamcinolone acetonide, including 74 with intravitreal triamcinolone acetonide 4 mg primary therapy. Cataract progression was defined in some articles (> 2 score on LOCS) while others simply stated that progression was seen in a certain number of eyes.*

*For eyes receiving intravitreal triamcinolone acetonide, 12.0% (range 2.8% to 32.0% across all doses) were noted to have cataract progression. Similarly, eyes treated with intravitreal triamcinolone acetonide 4 mg primary or adjunctive therapy had a rate of cataract progression of 14.4% and 13.6%, respectively and was similar to eyes receiving periocular injection (10.1%). In articles which defined the type of cataract, the majority of cataracts observed were posterior subcapsular (PSC) (8.9%), while cortical and nuclear cataracts were reported at a much lower frequency (1.2% and 2.1%, respectively).*

**Table 7.1.3 E – Study C-06-26**
**(Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)**

**Intravitreal Route**
**All Adverse Events – Overall Safety Population**

| Coded Event | Triamcinolone Acetonide N = 60 | |
|---|---|---|
| | N | % |
| **Cataract** | 1 | 1.7 |
| **Macular Edema** | 1 | 1.7 |
| **Intraocular Pressure Increase** | 5 | 8.3 |

**Reviewer's comments:**

*No patients exposed to triamcinolone acetonide were reported to have experienced a serious adverse event or discontinued from the study due to an adverse event. Overall, a review of adverse events revealed no untoward safety issues based upon the assessment of adverse events characteristics (incidence, onset, duration, relationship to therapy, and impact upon continuing participation in the study).*

*The safety and efficacy effects seen with this product are class effects related to ophthalmic steroids.*

*Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.*

*Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.*

## 7.1.4 Other Search Strategies

There were no unique or special safeties studies found necessary or conducted.

## 7.1.5 Common Adverse Events

Refer to section 7.1.2

### 7.1.6 Less Common Adverse Events

Refer to section 7.1.2

### 7.1.7 Laboratory Findings

There is no preclinical data or clinical data presented or referenced that indicate triamcinolone acetonide adversely affects blood chemistry, hematology, or urinalysis.

### 7.1.8 Vital Signs

There is no preclinical data or clinical data presented or referenced that indicate triamcinolone acetonide adversely affects pulse, blood pressure, or respiration.

### 7.1.9 Electrocardiograms (ECG)

There is no preclinical data or clinical data presented or referenced that indicate triamcinolone acetonide adversely affects cardiac conduction.

### 7.1.10 Immunogenicity

No immunogenicity studies were performed by the applicant.

### 7.1.11 Human Carcinogenicity

No carcinogenicity studies were performed by the applicant.

### 7.1.12 Special Safety Studies

No special safety studies were performed by the applicant.

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Triamcinolone is injected intravitreally into the eye. There is no potential for withdrawal phenomena or abuse potential.

### 7.1.14 Human Reproduction and Pregnancy Data

Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and the embryo or fetus.

### 7.1.15 Assessment of Effect on Growth

Assessment of effect on growth was not studied by the applicant. The efficacy and safety of corticosteroids in the pediatric population are based on the well-established use of triamcinolone acetonide.

### 7.1.16 Overdose Experience

Triamcinolone is injected intravitreally into the eye. There is no potential for overdose.

### 7.1.17 Postmarketing Experience

No post marketing studies are planned or are recommended.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

The total dataset for safety evaluation consisted of 18,653 eyes and 13,983 patients receiving any treatment in Study C-06-26 plus an additional 60 eyes were enrolled into the efficacy and safety data base from clinical study C-05-62.

#### 7.2.1.2 Demographics

Triamcinolone acetonide injectable suspension is therapeutically equivalent to a marketed product KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ). Kenalog-40 has been marketed product for approximately 40 years. There is adequate safety information by gender, ethnicity, age, and underlying disease process.

#### 7.2.1.3 Extent of exposure (dose/duration)

In Study C-06-26, 18,653 eyes were dosed with triamcinolone acetonide with the intravitreal dose ranging from 1 to 4 mg. and the periocular dose ranging from 1 to 40 mg. In Study C-05-62, 60 eyes were dosed with intravitreal triamcinolone from 1 to 20 mg. There is adequate extent of exposure with the proposed drug product.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

All clinical data sources provided in the New Drug Application were utilized in the review of safety for this product. This includes the major sources of clinical data utilized in this review:

- Literature references citing the use of the product Triamcinolone Acetonide Injectable Suspension in Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report)
- Data from Clinical trial C-05-62 (Title: Clinical Evaluation of the Safety and Efficacy of Preservative-Free Triamcinolone Acetonide Sterile Suspension for Visualization During Vitreoretinal Surgery)
- A 120 Day Safety Update Report for clinical trial C-05-62 and a new literature search for the meta-analysis study C-06-26 for articles published Jan. 1, 2007 to Sept. 5, 2007 was submitted Sept. 28, 2007 (the original meta-analysis study, C-06-26, performed a literature search for articles published from 1960 to Feb. 14, 2007.)

### 7.2.2.1 Other studies

All clinical data sources provided in the New Drug Application were utilized in the review of safety for this product.

### 7.2.2.2 Postmarketing experience

Triamcinolone acetonide injectable suspension is therapeutically equivalent to a marketed product KENALOG®-40 (NDA 14-901, Bristol-Myers, Squibb, Princeton, NJ). Kenalog-40 has been a marketed product in the U.S. for approximately 40 years.

### 7.2.2.3 Literature

The literature search for the meta-analysis study C-06-26 was performed for articles published from 1960 to Feb. 14, 2007. Additionally, a 120 Day Safety Update Report for clinical trial C-05-62 and a new literature search for the meta-analysis study C-06-26 for articles published Jan. 1, 2007 to Sept. 5, 2007 was submitted Sept. 28, 2007.

## 7.2.3 Adequacy of Overall Clinical Experience

There is adequate clinical experience with the proposed drug product, triamcinolone acetonide. Triamcinolone acetonide, the active ingredient, has been marketed as Kenalog-40 in the United States for over 40 years.

The dose and duration of the drug used in the cited literature and safety surveys were adequate to determine safety for the intended use.

There is adequate safety information by gender, ethnicity, age, and underlying disease process.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No *in vivo – in vitro* correlation studies were conducted with triamcinolone Acetonide.

### 7.2.5 Adequacy of Routine Clinical Testing

There is adequate clinical experience with the proposed drug product, triamcinolone acetonide. Triamcinolone acetonide, the active ingredient, has been marketed as Kenalog-40 in the United States for over 40 years.

There is adequate routine clinical testing reported in the literature (study C-06-26), clinical trial C-05-62, and the 120 Day Safety Update report.

### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There is adequate clinical experience with the proposed drug product, triamcinolone acetonide.

A considerable body of information has been reported in the literature on the absorption, distribution, metabolism and excretion of triamcinolone acetonide in humans. Extensive clinical experience is evident in a review of published literature dating back to the 1960's and demonstrates that triamcinolone acetonide is safe, well-tolerated and effective for a variety of ophthalmic indications.

### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There has adequate evaluation for potential adverse events for this drug and for drugs in this class, and there are no recommendations for further study.

### 7.2.8 Assessment of Quality and Completeness of Data

The data submitted for the assessment of safety for triamcinolone acetonide is adequate. There is a large amount of information provided in the meta-analysis (study C-06-26). Clinical trial C-05-62 and the 120 Day Safety Update Report were provided. For clinical study C-05-62 videos of pre and post installation of the drug product were reviewed for completeness and to document the benefit of triamcinolone acetonide for visualization during a vitrectomy.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety and efficacy effects seen with this product are class effects related to ophthalmic steroids.

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should not be used in active ocular herpes simplex.

Endophthalmitis, eye inflammation, increased intraocular pressure and visual disturbances including vision loss have been reported with intravitreal administration.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled data vs. individual study data

Study report C-06-26 and study C-05-62 were not pooled because study C-06-26 is a meta-analysis of 18,653 eyes and 13,983 patients receiving any treatment in approximately 300 articles, while study C-05-62 is a single trial of 60 eyes for visualization of the retina during a vitrectomy (intraoperative results).

#### 7.4.1.2 Combining data

The frequency of adverse events/reactions is presented in the Tables in Section 7.1.3.

### 7.4.2 Explorations for Predictive Factors

There is adequate clinical experience with the proposed drug product, triamcinolone acetonide No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

Safety and effectiveness in pediatric patients have been established.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established use of triamcinolone acetonide. The use of triamcinolone acetonide in the pediatric population would be unlikely since the diseases indicated rarely occur in the pediatric population.

### 7.4.3 Causality Determination

**Reviewer's comments:**

*This review has not revealed demographic effects on the safety profile. The adverse events noted are similar to those for this class of drugs.*

# 8 ADDITIONAL CLINICAL ISSUES

## 8.1 Dosing Regimen and Administration

The meta-analysis, study C-06-26, citied articles with the route of drug administration varying from intravitreal to periocular routes (Sub-Tenon's or retrobulbar) with the dose ranging from 1 to 40 mg of triamcinolone acetonide.

For the treatment of ophthalmic conditions the initial recommended dose of Triescence is 4 mg (100 µl of 40 mg/mL suspension) administered intravitreally with subsequent dosage of 4 mg (100 µl of 40 mg/mL suspension) as needed over the course of treatment.

For visualization during vitrectomy **t**he recommended dose of Triescence is 1 to  mg (100 µl of 40 mg/mL suspension) administered intravitreally.

## 8.2 Drug-Drug Interactions

Specific drug interaction studies are not reported. No additional adverse drug-drug interactions were noted in the literature review.

## 8.3 Special Populations

No overall differences in safety or effectiveness have been observed between elderly and other adult patients. There are no overall differences in safety or effectiveness with regards to gender or ethnicity.

## 8.4 Pediatrics

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established use of triamcinolone acetonide.

## 8.5 Advisory Committee Meeting

No Advisory Committee was necessary or convened for this drug product.

## 8.6 Literature Review

Literature references cited the use of the product Triamcinolone Acetonide Injectable Suspension in Clinical study report C-06-26, a meta-analysis of 300 peer-reviewed articles (299 articles plus one study group report). On Sept. 28, 2007 a 120 Day Safety Update Report for clinical trial C-05-62 and a new literature search for the meta-analysis study C-06-26 for articles published Jan. 1, 2007 to Sept. 5, 2007 was submitted.

**Reviewer's Comments:**

*A literature search conducted by this reviewer failed to identify any significant literature references not cited by the applicant for this New Drug Application.*

## 8.7 Postmarketing Risk Management Plan

There are no recommended Phase 4 clinical study commitments.

## 8.8 Other Relevant Materials

The Division of Medication Errors and Technical Support (DMETS) was consulted on June 22, 2007, regarding the proposed use of the tradename, Triescence.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) was consulted on June 22, 2007, regarding the proposed labeling.

Labeling recommendations, where appropriate, were incorporated into the labeling review.

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

There is over a 40 year history of use of the active ingredient, triamcinolone acetonide, in the United States (marketed by Bristol-Myers, Squibb, Princeton, NJ, as KENALOG-40) with adequate demonstration of safety as determined in this clinical review and for effectiveness of sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and for visualization during a vitrectomy.

## 9.2 Recommendation on Regulatory Action

It is recommended that NDA 22-048 be approved for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and visualization during a vitrectomy with the labeling revisions listed in this review.

The application supports the safety and effectiveness for sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids and visualization during a vitrectomy.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

There are no recommended Phase 4 clinical study commitments.

### 9.3.2 Required Phase 4 Commitments

There are no recommended Phase 4 clinical study commitments.

### 9.3.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests.

## 9.4 Labeling Review

See the Line-by-Line Labeling review, Section 10.2.

## 9.5 Comments to Applicant

# 10 APPENDICES

## 10.1 Review of Individual Study Reports

See Section 6.1 of this review.

## 10.2 Line-by-Line Labeling Review

Following is Alcon's proposed labeling submitted with the new drug application on May 29, 2007, and amended in the 120 Day Safety Update submitted Sept. 28, 2007.


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/s/
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Martin Nevitt
11/27/2007 11:20:28 AM
MEDICAL OFFICER

William Boyd
11/27/2007 11:28:23 AM
MEDICAL OFFICER