CENTER FOR DRUG EVALUATION AND RESEARCH

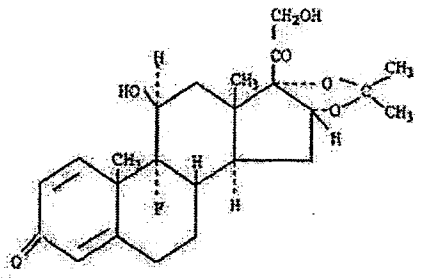
APPLICATION NUMBER:

NDA 22-220

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	000
Submission Code	Original
Letter Date	August 15, 2007
Stamp Date	August 16, 2007
PDUFA Goal Date	June 16, 2008
Reviewer Name	William M. Boyd, M.D.
Review Completion Date	May 20, 2008
Established Name	triamcinolone acetonide injectable suspension, 80 mg/mL
(Proposed) Trade Name	Trivaris
Therapeutic Class	corticosteroid
Applicant	Allergan, Inc.
Priority Designation	S
Formulation	Active ingredient: triamcinolone acetonide
Structure	$C_{24}H_{31}FO_6$



(Proposed) Dosing Regimen	initial dose of triamcinolone acetonide injectable suspension, 80 mg/mL may vary from 2.5 mg to 100 mg per day depending on the specific disease entity being treated
(Proposed) Indications	See below

Ophthalmic Use:

- Sympathetic ophthalmia,
- Temporal arteritis,
- Uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

Intramuscular Use:

Where oral therapy is not feasible as follows: allergic states, dermatologic diseases, endocrine disorders, gastrointestinal diseases, hematologic disorders, miscellaneous, neoplastic diseases, nervous system, renal diseases, respiratory diseases, and rheumatic disorders.

Intra-articular Use:

Adjunctive therapy for short-term administration in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

(Proposed) Intended Population	Subjects with the conditions cited above for ophthalmic, intramuscular and intra-articular indications

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-220 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL for:

1) Ophthalmic Use
Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL is indicated for:

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

2) Intramuscular Use
Where oral therapy is not feasible, Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL is indicated for intramuscular use as follows:

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukemias and lymphomas.

Nervous system: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

3) Intra-Articular Use
The intra-articular or soft tissue administration of Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

There are no recommendations for additional postmarketing studies.

1.2 Risk Benefit Assessment

There is over a 50 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.

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert. KENALOG-40 is a sterile aqueous suspension containing triamcinolone acetonide at a concentration of 40 mg/mL, benzyl

alcohol at a concentration of 0.9% (w/v) as a preservative, and excipients. The KENALOG-40 package insert contains warnings regarding the use of benzyl alcohol in pediatric patients.[1]

The literature describes an acceptable safety profile for the use of the intravitreal KENALOG-40 to treat ocular inflammatory conditions that are unresponsive to topical steroids. However, one complication associated with intravitreal injections is the rare (about 1%) but clinically meaningful occurrence of noninfectious endophthalmitis which is anecdotally related to benzyl alcohol, the preservative in the KENALOG-40 formulation.

Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL is a preservative-free formulation of triamcinolone acetonide specifically intended for intravitreal administration.

The safety issues seen with this drug product are class issues for systemically administered corticosteroids. See Section 2.4 for an extensive list of important safety issues.

1.3 Recommendations for Postmarketing Risk Management Activities

There are no recommended Phase 4 clinical study commitments.

1.4 Recommendations for other Post Marketing Study Commitments

There are no optional or recommended Phase 4 requests.

[1] This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome", (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

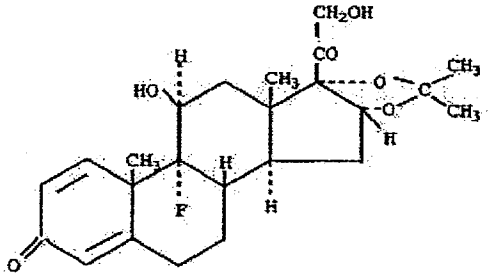
2 Introduction and Regulatory Background

2.1 Product Information

Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL is a synthetic glucocorticoid corticosteroid . This formulation is suitable for intravitreal, intra-muscular, and intra-articular use. This formulation is not for intravenous injection.

Each syringe of the sterile aqueous gel suspension contains 8 mg triamcinolone acetonide in 0.1 mL (8% suspension) in a vehicle containing w/w percents of 2.3% sodium hyaluronate; 0.63% sodium chloride; 0.3% sodium phosphate, dibasic; 0.04% sodium phosphate, monobasic; and water for injection. Trivaris is preservative-free with a pH of 7.0 to 7.4.

The chemical name for triamcinolone acetonide is 9α-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. Its structural formula is:



MW 434.50 with a molecular formula of $C_{24}H_{31}FO_6$. Triamcinolone acetonide occurs as a white to cream-colored crystalline powder having not more than a slight odor, and is practically insoluble in water and very soluble in alcohol.

Quantitative Composition for Trivaris

Ingredient	Concentration, %w/w	Concentration, mg/g	Quantity per Dose, mg
Triamcinolone acetonide	8.0	80	4.0
Sodium hyaluronate	2.3	23	1.2
Sodium chloride	0.63	6.3	0.32
Dibasic sodium phosphate, heptahydrate	0.30	3.0	0.15
Monobasic sodium phosphate, monohydrate	0.04	0.4	0.02
WFI	qs ad 100	qs ad 1000	qs ad 50

Source: Allergan Table 3.2.P.1.2-1 Quantitative Composition for TRIVARIS (9634X)

Proposed Trivaris Product Specifications

Test Parameter	Final (In-House) Batch Release	Regulatory and Product Shelf Life	Method
Triamcinolone Acetonide (AGN 206230)			
Impurities (%w/w of triamcinolone acetonide): **Specified and Identified:** **Individual Unspecified:** **Total Impurities:**	 NMT NMT NMT	 NMT NMT NMT	
Triamcinolone Acetonide ID	Positive for triamcinolone acetonide	Not tested	
pH	7.0 – 7.4	7.0 – 7.4	USP <791>
Particle Size			
Physical Appearance			
Microscopic Appearance,			
Foreign Particulate Matter, USP <788>			
Content Uniformity, USP <905>	Meets test requirements	Meets test requirements	
Sterility, USP	Meets test requirements	Meets test requirements	USP <71>
Endotoxins, LAL	NMT	NMT	USP <85>

b(4)

Source: Allergan Table 3.2.P.5.1.2-1 Proposed Product Specifications for TRIVARIS (9634X) 1/21/08 submission

2.2 Currently Available Treatments for Proposed Indications

Kenalog-40 (NDA 14-901) is approved and marketed for the indications cited in Section 1.1 of this review and in the revised labeling attached to this review.

Triesence (triamcinolone acetonide injectable suspension) 40 mg/mL (NDA 22-048) is approved for the treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal

arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids; unlike Kenalog-40, it is also approved for visualization during vitrectomy.

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) 40 mg/mL (NDA 22-048, Alcon, Inc.) is a sterile, ——————→ nonpreserved, single-dose, injectable ophthalmic suspension containing 40 mg/mL of triamcinolone acetonide which is pharmaceutically and therapeutically equivalent to the marketed product KENALOG-40 (NDA 14-901, Bristol-Myers, Squibb). The concentration of 40 mg/mL of triamcinolone acetonide is the same as that in KENALOG-40. b(4)

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

2.4 Important Safety Issues with Consideration to Related Drugs

The safety issues seen with this drug product are class issues for systemically administered corticosteroids. Per the class labeling for corticosteroid products:

Because Trivaris is a suspension, it should not be administered intravenously. Strict aseptic technique is mandatory.

Alterations in Endocrine Function
Corticosteroids can produce Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Mineralocorticoid supplementation is of particular importance in infancy.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Increased Risks Related to Infections
Corticosteroids may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections. The degree to which the dose, route and duration of corticosteroid administration correlates with the specific risks of infection is not well characterized, however, with increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Corticosteroids may mask some signs of infection and may reduce resistance to new infections.

Corticosteroids may exacerbate infections and increase risk of disseminated infection.

The use of Trivaris in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

Chickenpox and measles can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In children or adults who have not had these diseases, particular care should be taken to avoid exposure. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions.

Corticosteroids may increase risk of reactivation or exacerbation of latent infection.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Corticosteroids should not be used in cerebral malaria.

Alterations in Cardiovascular/Renal Function
Corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. These effects are less likely to occur with the synthetic

derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. These agents should be used with caution in patients with hypertension, congestive heart failure, or renal insufficiency.

Literature reports suggest an association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with caution in these patients.

Use in Patients with Gastrointestinal Disorders
There is an increased risk of gastrointestinal perforation in patients with certain GI disorders. Signs of GI perforation, such as peritoneal irritation, may be masked in patients receiving corticosteroids.

Corticosteroids should be used with caution if there is a probability of impending perforation, abscess or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; and active or latent peptic ulcer.

Ophthalmic Effects
Prolonged 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 fungi or viruses.

The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes.

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids **should not be used in active** ocular herpes simplex.

Behavioral and Mood Disturbances
Corticosteroid use may be associated with central nervous system effects ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Decrease in Bone Density
Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal

women) before initiating corticosteroid therapy and bone density should be monitored in patients on long term corticosteroid therapy.

Vaccination
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered, however, the response to such vaccines can not be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

Effect on Growth and Development
Long-term use of corticosteroids can have negative effects on growth and development in children.

Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully monitored.

Use in Pregnancy
Prednisolone can cause fetal harm when administered to a pregnant woman. Human and animal studies suggest that use of corticosteroids during the first trimester of pregnancy is associated with an increased risk of orofacial clefts, intrauterine growth restriction and decreased birth weight. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Neuromuscular Effects
Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Kaposi's Sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pre-NDA meeting was held on March 23, 2007, for NDA 22-220 (IND —). Allergan proposed to submit this an NDA under section 505(b)(2) of the Act. This application would rely in part on published literature, and also in part on the Agency's previous finding of safety and effectiveness for triamcinolone under NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP).

At this meeting, the Agency agreed that the 505(b)(2) filing and published literature should be adequate to support the efficacy of triamcinolone acetonide for the currently approved indications in the Kenalog-40 label.

On August 15, 2007, Allergan submitted a 505(b) (2) application cross-referencing information from NDA 14-901 (KENALOG -40) requesting a 6 month priority review. Allergan requested priority review status claiming that their product was a substantial improvement over the marketed KENALOG -40 product because it is non-preserved, has a narrower pH range of 7.0-7.4, and is a more homogenous suspension. A standard review was granted.

The proposed labeling was based on that of the referenced application, NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP).

2.6 Other Relevant Background Information

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

- Agency's previous finding of safety and effectiveness found in the labeling (package insert) for triamcinolone acetonide under NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP).
- Report s from two ongoing phase 3 clinical trials that utilize the Trivaris formulation

- Literature search conducted by Allergan to identify published clinical articles on the administration of triamcinolone by the intraocular and intravitreal routes.

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

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with accepted clinical and ethical standards.

3.3 Financial Disclosures

Financial disclosure information has been provided by Allergan, Inc. for all investigators from two ongoing phase 3 clinical trials that utilize the Trivaris formulation.

Unmasked safety data from these 2 ongoing phase 3 clinical trials that utilize the Trivaris formulation are provided to further support the safety of Trivaris for intravitreal administration.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1 this review.

4.2 Clinical Microbiology

Not applicable to this review.

4.3 Preclinical Pharmacology/Toxicology

Triamcinolone acetonide is a synthetic corticosteroid with anti-inflammatory activity. Triamcinolone acetonide is currently marketed under the trade name Kenalog®-40. The current NDA is a 505(b)(2) submission. The application relies on published literature for safety and effectiveness and on the Agency's previous finding of safety and effectiveness for triamcinolone acetonide.

In ocular PK studies in NZW rabbits, following an ITV administration, high exposures to triamcinolone acetonide (TA) were seen in the vitreous humor and retina. The 4% triamcinolone acetonide prototype formulation generated similar intraocular triamcinolone acetonide concentrations compared to Kenalog-40 at the same dose. The systemic exposure to TA following ITV injection was very low.

In two ocular toxicity studies with triamcinolone acetonide, reversible ocular findings, including congestion, swelling and/or ocular discharge and tearing, were seen in both drug- and vehicle-treated animals, suggesting that the findings might be related to the injection procedure. From the two ocular toxicity studies, it was concluded that there was no toxicologically significant, drug-related toxicity with triamcinolone acetonide by intravitreal injection.

Triamcinolone acetonide was positive in the *in vivo* micronucleus test with triamcinolone acetonide in mice.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt retaining properties, are used as replacement therapy in adrenocortical deficiency states. Synthetic analogs such as triamcinolone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the bio-synthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Corticosteroids are capable of producing a rise in intraocular pressure.

Intravitreal corticosteroids can down regulate the production of proinflammatory mediators, and can be used in ocular inflammatory conditions.

4.4.2 Pharmacokinetics

Aqueous humor pharmacokinetics of triamcinolone acetonide were assessed in 5 patients following a single intravitreal administration (4 mg) of triamcinolone acetonide. Aqueous humor samples were obtained from 5 patients (5 eyes) via an anterior chamber paracentesis on Days 1, 3, 10, 17 and 31 post-injection. Peak aqueous humor concentrations of triamcinolone acetonide ranged from 2,151 to 7,202 ng/mL, the half-life ranged from 76 to 635 hours, and the area under the concentration-time curve (AUC_{0-t}) ranged from 231 to 1,911 ng·h/mL. The mean elimination half-life was 18.7 ± 5.7 days in 4 nonvitrectomized eyes (4 patients). In a patient who had undergone vitrectomy (1 eye), the elimination half-life of triamcinolone acetonide was much faster (3.2 days) relative to patients that had not undergone vitrectomy.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Type of Study	Study Identifier	Type, Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) dosage regimen route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
efficacy	9633-JAEB	ongoing	long-term efficacy and safety	randomized, active controlled	gel suspension, 1 mg 4 mg, repeated dosing, intravitreal	693[a]	patients with DME	3 years
efficacy	9633-SCORE	ongoing	long-term efficacy and safety	randomized, active controlled	gel suspension, 1 mg 4 mg, repeated dosing, intravitreal	461[a]	patients with central and branch RVO	3 years

[a] Based on interim data.
DME = diabetic macular edema; RVO = retinal vein occlusion.

Source: Allergan Table 5.2 - Tabular Listing of All Clinical Studies

The application requests approval for Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL for the currently approved ophthalmic indications in the KENALOG-40 label. The application relies on the Agency's previous finding of safety and effectiveness for triamcinolone acetonide under NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP) and on published literature.

Unmasked safety data from 2 ongoing phase 3 clinical trials that utilize the Trivaris formulation are provided to further support the safety of Trivaris for intravitreal administration.

5.2 Review Strategy

The August 15, 2007, submission was submitted electronically. All subsequent amendments were submitted electronically. All study reports were reviewed. The included clinical study

reports, literature review, and package insert for the reference drug product KENALOG-40 formed the basis for the review of safety for the proposed indications.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

5.3 Discussion of Individual Studies

This 505(b)(2) application relies on the Agency's previous finding of safety and effectiveness for triamcinolone acetonide under NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP).

Unmasked safety data from two ongoing phase 3 clinical trials that utilize the Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL formulation are provided to further support the safety of Trivaris for intravitreal administration.

Reviewer's Comments:

These two phase 3 trials are ongoing; the study protocols submitted are not full study reports and are not final.

A 120-day Safety Report dated December 17, 2007, contains interim safety tables for JAEB and SCORE. Case Report Forms are not provided; no interim study report is provided.

These interim safety tables were received by Allergan from the Jaeb Center and from the Score Study Group, respectively. Allergan states it has not analyzed the data in any way since the trials are ongoing.

5.3.1 9633 JAEB - A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema

Primary Objectives

- To determine whether intravitreal triamcinolone acetonide injections at doses of 1mg or 4mg [redacted] than macular laser photocoagulation in the treatment of diabetic macular edema. b(4)
- To compare the efficacy and safety of the 1mg and 4mg triamcinolone acetonide doses.

In the trial, 4mg and 1mg doses will be evaluated. The former will be used because it is the dose that is currently most commonly used in clinical practice and the latter because [redacted]

A. Study Design
Randomized, multi-center clinical trial.

B. Major Eligibility Criteria

- Age >=18 years.
- Study eye with best corrected E-ETDRS acuity >= 24 letters (20/320 or better) and <=73 letters (20/40 or worse).
- Study eye with center-involved DME present on clinical exam and on OCT.
- Fellow eye either eligible or has acuity >=19 letters (20/400 or better) and has not been previously treated with intravitreal corticosteroids.

C. Treatment Groups
Randomization to one of three treatment groups:

1) Standard of care group: conventional treatment consisting of focal/grid photocoagulation.
2) Intravitreal injection of 1mg of triamcinolone acetonide.
3) Intravitreal injection of 4mg of triamcinolone acetonide.

Patients may have one or two study eyes. Patients with two study eyes will receive photocoagulation in one eye and intravitreal triamcinolone acetonide, 1mg or 4mg dose, in the other eye. Patients and investigators will be masked to the triamcinolone acetonide dose (1mg or 4mg).

D. Duration of Follow-Up: Three years.

E. Main Efficacy Outcomes
Primary: Visual acuity (measured with E-ETDRS)
Secondary: Retinal thickening (measured on OCT)

F. Main Safety Outcomes
(1) Intraocular pressure elevation/glaucoma, (2) cataract, (3) endophthalmitis (bacterial or inflammatory), (4) retinal detachment.

G. Timing of Outcome Assessments
Primary outcome at 3 years (preliminary outcome assessment at 1 year).

H. Sample Size:
813 eyes (approximately 689 patients assuming 18% of the patients have two study eyes).

I. Schedule of Study Visits and Examination Procedures

	Study Month									
	0	4	8*	12*	16*	20*	24*	28*	32*	36
E-ETDRS visual acuity[a]	x	x	x	x	x	x	x	x	x	x
Fundus photos	7F	3F		7F			7F			7F
OCT[b]	x	x	x	x	x	x	x	x	x	x
IOP	x	x	x	x	x	x	x	x	x	x
Eye Exam[c]	x	x	x	x	x	x	x	x	x	x
Blood pressure	x			x			x			x
HbA1c[d]	x			x			x			x
Fluor. Angio[e]	x									
PK Blood Draws[f]	x	x								

Testing is on both eyes at each visit unless otherwise specified below.

a=includes protocol refraction at 0, 4, 12, 24, and 36 months. E-ETDRS refers to electronic ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.[56]

b=performed on both eyes at 0 (performed twice), 4, 12, 24, and 36 months and on the study eye only at other visits

c=includes lens assessment using standard photos at 0, 4, 12, 24, and 36 months (selected sites will obtain lens photos with Neitz and slit lamp cameras)

d=does not need to be repeated if HbA1c and lab normal values are available from within the prior 3 months (at baseline, can be performed within 3 weeks after randomization)

e=does not need to be performed if not part of usual care.

f= only at selected sites for patients randomized to either of the triamcinolone acetonide treatment groups.

*visit window may be extended if necessary for visit to occur no sooner than 3.5 months from the last treatment

5.3.2 9633 SCORE - The Standard Care vs. COrticosteroid for REtinal Vein Occlusion (SCORE) Study

Two Randomized Trials to Compare the Efficacy and Safety of Intravitreal Injection(s) of Triamcinolone Acetonide with Standard Care to Treat Macular Edema: One for Central Retinal Vein Occlusion and One for Branch Retinal Vein Occlusion

Primary Objectives

The primary objective of the SCORE Study is to compare visual acuity outcome among 3 groups of participants: those who are randomly assigned to receive standard care and those randomly

assigned to receive one of two doses of intravitreal injection(s) of triamcinolone acetonide for treatment of macular edema associated with CRVO and BRVO.

A. Study Design
Randomized, multi-center clinical trial.

B. Major Eligibility Criteria

- Age >=18 years.
- Study eye with ETDRS visual acuity score of greater than or equal to 19 letters (approximately 20/400) and less than or equal to 73 letters (approximately 20/40) by the ETDRS visual acuity protocol.
- Study eye with center-involved macular edema secondary to either CRVO or BRVO
- Mean retinal thickness on two OCT measurements greater than or equal to 250 microns (central subfield).

C. Treatment Groups

1. Standard care group: conventional treatment consisting of:
    a. CRVO:
        i. Observation of macular edema.
    b. BRVO:
        i. Study eyes with dense macular hemorrhage: Immediate observation. Grid laser photocoagulation will be performed if and when clearance of hemorrhage permits grid laser photocoagulation.
        ii. Study eyes without dense macular hemorrhage: Immediate grid laser photocoagulation.

2. Intravitreal injection(s) of 4 mg of triamcinolone acetonide,

3. Intravitreal injection(s) of 1 mg of triamcinolone acetonide.

Patients and investigators will be masked to the triamcinolone acetonide dose used (1 mg o 4 mg).

D. Duration of Follow-Up: Three years.

E. Main Efficacy Outcomes
Primary:

Improvement by 15 or more letters from baseline in best-corrected ETDRS visual acuity score at the 12-month visit as determined by the ETDRS visual acuity protocol.

Secondary:

- Change between baseline and each efficacy outcome assessment visit in best corrected ETDRS visual acuity score (e.g., mean change from baseline in visual acuity, distribution of change from baseline in visual acuity based on clinically meaningful cut points of improvement or worsening of visual acuity).
- Change in calculated retinal thickening as assessed by [redacted]
- Change in area of retinal thickening as assessed by stereoscopic color fundus photography.

F. Main Safety Outcomes
Specific safety outcomes include:

- Injection-related events including infectious endophthalmitis, non-infectious endophthalmitis, retinal tear or detachment, vitreous hemorrhage, ocular discomfort/irritation, ocular tenderness, ocular itching sensation, foreign body sensation, blurred vision, floaters, corneal abrasion, subconjunctival hemorrhage, conjunctival edema, and conjunctival hyperemia/erythema.
- Steroid-related toxicities including cataract and elevated IOP.

G. Timing of Outcome Assessments
Primary outcome at 12 months.

The SCORE Study consists of two separate independent clinical trials - one for CRVO and one for BRVO. Each of these clinical trials has its own overall Type I error (alpha) = .05.

H. Sample Size:
N = 162 within each study arm for each trial (i.e., BRVO = 486 total, CRVO = 486 total).

I. Schedule of Study Visits and Examination Procedures

	Baseline	4-month interval follow-up visits									Safety[2]	
		M4	M8	M12	M16	M20	M24	M28	M32	M36	D4	M1
Informed consent	X											
Urine pregnancy test	X[3]											
Medical/ocular history	X[3]											
Blood pressure	X[3]			X			X			X		
Visual acuity	X[4,5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[7]	X[7]
Manifest refraction	X[5]	X[5]		X[5]			X[5]			X[5]		
IOP	X[3,5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[7]	X[7]
Ophthalmic examination[8]	X[3,5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[7]	X[7]
Lens assessment[9]	X[3,5]	X[5]		X[5]			X[5]			X[5]		
Fundus photos Study Eye	M7F[3]	M3F	M3F	M7F	M3F	M3F	M7F	M3F	M3F	M7F		
Non-study Eye	M3F[3]			M3F			M3F			M3F		
FA	X[3]	X		X			X					
OCT	X[5,10]	X[5]	X[6]	X[5]	X[6]	X[6]	X[5]	X[6]	X[6]	X[5]		
Steroid injection /Laser[1]		X	X	X	X	X	X	X	X			

M= month
Q= every
D= day

M7F= Modified 7-Field photos
M3F= Modified 3-Field photos

1 Retreatment with steroid injections or laser photocoagulation (if applicable) should be administered at 4-month intervals unless there are specific reasons not to treat in which case the investigator may decide to postpone treatment (see protocol section 4.8.3).
2 Safety visits are performed at Day 4 and Month 1 after each injection.
3 To be performed within 21 days prior to randomization.
4 To be performed within 8 days prior to randomization
5 Examination data to be collected on both eyes.
6 Examination data to be collected on study eye only.
7 Examination data to be collected on the injected eye only.
8 Examination includes both a dilated fundus examination and a slit-lamp examination.
9 To be performed using the modified AREDS lens grading system.
10 OCT measurements will be performed twice on the same day in both eyes. This will occur within 21 days prior to randomization.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Reviewer's Comments:

The reports from two ongoing phase 3 clinical trials that utilize the Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL formulation are provided to further support the safety of Trivaris for intravitreal administration.

b(4)

6.1.1 Methods

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

- Agency's previous finding of safety and effectiveness found in the labeling (package insert) for triamcinolone acetonide under NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP).
- Report s from two ongoing phase 3 clinical trials that utilize the Trivaris formulation
- Literature search conducted by Allergan to identify published clinical articles on the administration of triamcinolone by the intraocular and intravitreal routes.

6.1.2 Demographics

Reviewer's Comments:

The reports from two ongoing phase 3 clinical trials that utilize the Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL formulation are provided to further support the safety of Trivaris for intravitreal administration.

b(4)

9633 JAEB Demographics

Baseline Patient Data According to Treatment Group

	Laser N=330	1 mg N=256	4 mg N=254
Gender: Female - *(%)*	50%	47%	49%
Age (yrs) - *Median (25th, 75th percentile)*	63 (57, 69)	63 (58, 70)	63 (57, 69)
Race- *(%)*			
White	74%	73%	72%
African-American	9%	9%	10%
Hispanic or Latino	12%	13%	13%
Asian	2%	3%	2%
American Indian/ Alaskan Native	1%	1%	1%
Native Hawaiian/Other Pacific Islander	<1%	0	<1%
More than one race	<1%	<1%	0
Unknown/ not reported	2%	1%	2%
Diabetes Type- *(%)*			
Type 1	4%	5%	5%
Type 2	96%	95%	95%
Duration of Diabetes (years)-			
Median (25th, 75th percentile)	15 (9 ,21)	15 (9 ,21)	16 (10 ,22)
HbA1c[b] - *Median (25th, 75th percentile)*	7.5 (6.6 ,8.6)	7.5 (6.6 ,8.5)	7.6 (6.8 ,8.8)
Prior Laser Photocoagulation[a] – *(%)*	60%	60%	62%
Prior Panretinal Scatter Photocoagulation – *(%)*	16%	16%	17%
Intraocular Pressure (mmHg)			
Median (25th, 75th percentile) - mmHg	16 (13 ,18)	16 (13 ,18)	16 (14 ,18)
History of Ocular Hypertension – **(%)**			
No	99%	97%	98%
Yes, No treatment currently prescribed	0	1%	0
Yes, 1 topical medication currently prescribed	1%	2%	1%
Lens Status (clinical exam)- *(%)*			
Phakic	79%	79%	78%
Pseudophakic	21%	21%	22%

a. Randomization stratification variable.
b. Missing for 23, 13, and 26 in the laser, 1mg, and 4mg groups, respectively
Note: Patients with two study eyes are counted in one of the injection groups and in the modified-ETDRS group.

Source: Allergan Table 2.7.4.7-DME 1.01

9633 SCORE Demographics

		Total		Treatment group					
				1 mg		4 mg		SC	
		N	%	N	%	N	%	N	%
Total		594	100.0	196	100.0	200	100.0	198	100.0
Gender	Female	278	46.8	94	48.0	88	44.0	96	48.5
	Male	316	53.2	102	52.0	112	56.0	102	51.5
Race	Asian	10	1.7	4	2.0	4	2.0	2	1.0
	Black	34	5.7	16	8.2	11	5.5	7	3.5
	More than one race	4	0.7	0	0.0	3	1.5	1	0.5
	Native Hawaiian or other Pacific Islander	1	0.2	0	0.0	1	0.5	0	0.0
	White	533	89.7	172	87.8	179	89.5	182	91.9
	Unable to specify	12	2.0	4	2.0	2	1.0	6	3.0
Ethnicity	Hispanic or Latino	32	5.4	11	5.6	5	2.5	16	8.1
	Not Hispanic or Latino	545	91.8	182	92.9	187	93.5	176	88.9
	Unknown	17	2.9	3	1.5	8	4.0	6	3.0
Iris Color	Blue	222	37.4	67	34.2	76	38.0	79	39.9
	Brown	227	38.2	76	38.8	76	38.0	75	37.9
	Green/Hazel	135	22.7	49	25.0	46	23.0	40	20.2
	Other	10	1.7	4	2.0	2	1.0	4	2.0

Source: Allergan Table 2.7.4.7-SCORE 1.01 Demographics

Characteristic		Treatment group		
		1 mg (n=196)	4 mg (n=200)	SC (n=198)
Baseline Age (yrs)	Mean	67	68	67
	SD	11	11	11
Screening E-ETDRS Visual Acuity (letters)	Mean	55	54	55
	SD	13	14	13
Baseline IOP (mm Hg)	Mean	15	15	15
	SD	3	3	3
1st Screening OCT (microns of central subfield)	Mean	535	520	537
	SD	171	164	162
Repeat Screening OCT (microns of central subfield)	Mean	530	516	537
	SD	163	163	161
Disease Duration (months)	Mean	4	5	4
	SD	4	4	4

Source: Allergan Table 2.7.4.7-SCORE 1.02 Demographics - Summary Statistics

6.1.3 Patient Disposition

Reviewer's Comments:

The reports from two ongoing phase 3 clinical trials that utilize the Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL formulation are provided to further support the safety of Trivaris for intravitreal administration.

b(4)

6.1.4 Analysis of Primary Endpoint(s)

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

6.1.5 Analysis of Secondary Endpoints(s)

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

6.1.6 Other Endpoints

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

6.1.7 Subpopulations

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

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.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

6.1.10 Additional Efficacy Issues/Analyses

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

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

- Agency's previous finding of safety and effectiveness found in the labeling (package insert) for triamcinolone acetonide under NDA 14-901, KENALOG-40 (triamcinolone acetonide injectable suspension, USP).
- Report s from two ongoing phase 3 clinical trials that utilize the Trivaris formulation
- Literature search conducted by Allergan to identify published clinical articles on the administration of triamcinolone by the intraocular and intravitreal routes.

7.1.2 Adequacy of Data

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

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 indications.

7.2.2 Explorations for Dose Response

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

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 indications.

7.2.3 Special Animal and/or In Vitro Testing

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

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 indications.

7.2.4 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 and in the submitted clinical trials JAEB and CORE.

7.2.5 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 indications.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

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.

7.3 Major Safety Results

7.3.1 Deaths

9633 JAEB Deaths

Ptid	Trt Group	Rand Date	Birth Date	Death Date	Possibly Related to Study Procedure	Cause of Death
B012-1[illegible]	Laser	7/11/05			No	Cardiac failure congestive and Acute respiratory distress syndrome
B028-7[illegible]	IVT	8/26/05			No	Myocardial infarction
B029-10[illegible]	IVT	4/18/06			No	Heart attack
B041-01[illegible]	Laser	3/11/05			No	Heart failure
B043-8[illegible]	IVT	5/16/05			No	Blood clot
B044-01[illegible]	IVT	7/15/04			No	Unknown
B044-10[illegible]	IVT	10/12/04			No	Unknown
B046-03[illegible]	Laser	3/25/05			No	Esophageal cancer
B048-08[illegible]	Both	2/3/05			No	Kidney failure
B048-10[illegible]	IVT	3/31/05			No	Metastatic lung disease
B062-1[illegible]	IVT	2/3/06			No	Myocardial infarction
B065-05[illegible]	Both	3/29/05			No	Coronary artery atherosclerosis
B067-16[illegible]	IVT	7/20/05			No	Cardiac arrest
B082-7[illegible]	Laser	6/27/05			No	Myocardial infarction
B088-22[illegible]	Both	3/1/06			No	Atherosclerotic coronary artery disease
B099-01[illegible]	Laser	2/28/05			No	Cardiopulmonary arrest, respiratory failure, osteomyelitis
B100-02[illegible]	Laser	10/25/04			No	Unknown
B101-[illegible]	Both	4/28/05			No	Congestive Heart Failure
B111-08[illegible]	Both	1/12/05			No	Colon cancer
B123-1[illegible]	Both	8/12/05			No	Heart/ Diabetes Complications
B123-[illegible]	Laser	4/18/05			No	Diabetes complications
B001-01[illegible]	IVT	10/21/04			No	Congestive Heart Failure
B022-13[illegible]	Laser	09/01/05			No	Respiratory/cardiac arrest
B035-4[illegible]	Both	11/15/05			No	Ovarian cancer
B064-10[illegible]	IVT	04/06/05			No	Massive stroke
B069-12[illegible]	IVT	04/18/06			No	Pulmonary embolism
B073-14[illegible]	IVT	03/06/06			No	Cardiac arrest
B080-22[illegible]	Both	03/22/06			No	Myocardial infarction
B091-16[illegible]	Both	10/21/05			No	Unknown
B111-02[illegible]	Laser	05/09/05			No	Myocardial infarction
B111-15[illegible]	IVT	05/16/05			No	Unknown
B111-27[illegible]	IVT	08/08/05			No	Heart attack
B129-01[illegible]	IVT	02/22/05			No	Unknown

b(6)

Source: Allergan Table 2.7.4.7-DME 2.06 Summary of Deaths (total for study)

7.3.2 Significant Adverse Events

9633 SCORE Significant Adverse Events

Treatment Assigned	Site No.	Subject ID	Event Description	Age (yrs)	Days from Last Injection	Severity	Related to Study Drug	Related to Procedure	Case Outcome	Outcome
1 mg	059	0002	*NEOVASCULAR GLAUCOMA*		104	MODERATE	NO	NO	SURGERY	COMPLETE RECOVERY
	126	0008	RETINAL DETACHMENT		145	SEVERE	NO	NO	SURGERY	COMPLETE RECOVERY
4 mg	002	0042	*NEOVASCULAR GLAUCOMA*		126	SEVERE	NO	NO	OTHER	ONGOING
	019	0003	*CUPPING OF OPTIC NERVE IN OS*		112	SEVERE	NO	NO	SURGERY	COMPLETE RECOVERY
	021	0006	*WORSENING OF PSC OS*		279	MILD	YES	NO	SURGERY	COMPLETE RECOVERY
	063	0010	*STERILE ENDOPHTHALMITIS*		98	MODERATE	NO	YES	REQ MEDS	ONGOING
	065	0001	*CATARACT SURGERY RIGHT EYE*		30	MODERATE	YES	NO	SURGERY	COMPLETE RECOVERY
	081	0010	*HIGH IOP*		7	SEVERE	NO	YES	SURGERY	ONGOING
	086	0004	*MACULAR HOLE*		28	MODERATE	NO	NO	SURGERY	ONGOING
	092	0002	*ENDOPHTHALMITIS*		3	SEVERE	NO	YES	SURGERY	COMPLETE RECOVERY
	124	0004	*ADVANCING CORTICAL CATARACT*		26	MILD	YES	NO	SURGERY	COMPLETE RECOVERY
Standard Care	032	0008	*INCREASE IOP*		497	MODERATE	NO	NO	SURGERY	ONGOING
	108	0001	*INCREASED CATARACT OD*		124	SEVERE	NO	YES	SURGERY	COMPLETE RECOVERY
	124	0013	*MACULAR ISCHEMIA*		61	SEVERE	NO	NO	OBSERVATION	ONGOING

b(6)

Source: Allergan Table 2.7.4.7-SCORE 2.03 Listing of Serious Ocular Adverse Events Study Eye Events in Italics - N = 14 events

7.3.3 Submission Specific Primary Safety Concerns

9633 JAEB IOP Elevation

APPEARS THIS WAY
ON ORIGINAL

Intraocular Pressure (IOP)	Treatment Group			
	Laser (N=330)	IVT 1mg (N=256)	IVT 4mg (N=254)	Nonstudy Eye Injected with Study Drug (N=22)
Increase >=10 mmHg from baseline at any visit	12 (4%)	39 (15%)	87 (34%)	4
IOP >=30 mmHg at any visit	4 (1%)	21 (8%)	52 (20%)	3
IOP-lowering meds prescribed for patient at any visit, not on IOP-lowering meds at baseline*	28 (8%)	36 (14%)	73 (29%)	7
Glaucoma diagnosis without surgery at any visit	0	0	3	0
Angle closure glaucoma diagnosis at any visit	0	0	2	0
Glaucoma surgery (filter or laser) at any visit	0	0	4	0

*9 eyes on IOP lowering medication at any followup visit were not counted because they were on IOP-lowering medication at baseline.

Source: Allergan Table 2.7.4.7-DME 2.07 Intraocular Pressure Elevation (includes eyes with at least 1 follow-up visit)

9633 JAEB Cataract Extraction

Number of eyes phakic at baseline	Laser N=262	IVT 1mg N=203	IVT 4mg N=197
Through 12 Month	12	14	13
Post-12 Month Through 24 Month	15	24	69
Post-24 Month	7	5	2
TOTAL	34 (13%)	43 (21%)	84 (43%)

Source: Allergan Table 2.7.4.7-DME 2.10 Cataract Extraction for Phakic Eyes

9633 SCORE Targeted Safety Events

APPEARS THIS WAY
ON ORIGINAL

Type of Event	Treatment Assignment			
	1 mg	4 mg	SC	All
Cataract Surgery	3	31	4	38
Glaucoma Surgery	3	4	.	7
Infectious endophthalmitis	.	1	.	1
IOP > 35 twice on max meds	.	.	.	.
Non-infectious endophthalmitis	.	1	.	1
Silicone oil in vitreous	51	32	2	85

Source: Allergan Table 2.7.4.7-SCORE 2.01 Summary of Targeted Ocular Safety Events in Study Eye

APPEARS THIS WAY
ON ORIGINAL

9633 SCORE IOP Elevation

APPEARS THIS WAY
ON ORIGINAL

Visit		Treatment Assignment					
		1 mg		4 mg		SC	
		N	%	N	%	N	%
4 Months	Total	167	100.0	160	100.0	157	100.0
	Change from Baseline						
	≤ 10 mm Hg	163	97.6	150	93.8	156	99.4
	> 10 mm Hg	4	2.4	10	6.3	1	0.6
8 Months	Total	134	100.0	132	100.0	131	100.0
	Change from Baseline						
	≤ 10 mm Hg	131	97.8	125	94.7	131	100.0
	> 10 mm Hg	3	2.2	7	5.3	.	.
12 Months	Total	109	100.0	108	100.0	106	100.0
	Change from Baseline						
	≤ 10 mm Hg	108	99.1	100	92.6	106	100.0
	> 10 mm Hg	1	0.9	8	7.4	.	.
16 Months	Total	84	100.0	78	100.0	77	100.0
	Change from Baseline						
	≤ 10 mm Hg	84	100.0	74	94.9	76	98.7
	> 10 mm Hg	.	.	4	5.1	1	1.3
20 Months	Total	58	100.0	58	100.0	52	100.0
	Change from Baseline						
	≤ 10 mm Hg	57	98.3	58	100.0	52	100.0
	> 10 mm Hg	1	1.7	.	.	.	.
24 Months	Total	37	100.0	33	100.0	26	100.0
	Change from Baseline						
	≤ 10 mm Hg	37	100.0	32	97.0	26	100.0
	> 10 mm Hg	.	.	1	3.0	.	.
28 Months	Total	16	100.0	15	100.0	10	100.0
	Change from Baseline						
	≤ 10 mm Hg	16	100.0	15	100.0	10	100.0
32 Months	Total	4	100.0	2	100.0	4	100.0
	Change from Baseline						
	≤ 10 mm Hg	4	100.0	2	100.0	4	100.0

Source: Allergan Table 2.7.4.7-SCORE 2.08 Increase from Baseline in IOP

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

9633 JAEB Ocular Adverse Events

APPEARS THIS WAY
ON ORIGINAL

Adverse Event	Laser (N=330)	IVT 1mg (N =256)	IVT 4mg (N =254)	Nonstudy Eye Injected with Study Drug (N =22)
Abnormal sensation in eye	5	9	8	1
Accommodation disorder	4	4	6	0
Acrochordon	0	0	1	0
Adenoviral conjunctivitis	1	0	0	0
Adverse event	0	2	0	0
Altered visual depth perception	2	0	1	0
Amaurosis fugax	0	0	1	0
Aneurysm	0	1	0	0
Angle closure glaucoma	0	0	2	0
Anterior capsule contraction	0	0	1	0
Anterior chamber cell	3	19	11	0
Anterior chamber flare	0	10	7	0
Asthenopia	2	1	0	0
Blepharal papilloma	1	0	0	0
Blepharitis	8	5	5	0
Blepharospasm	0	0	1	0
Blindness	1	0	0	0
Blindness transient	1	0	0	0
Burning sensation	0	1	0	1
Cataract	26	22	51	5
Cataract cortical	24	22	32	3
Cataract extraction	0	0	1	0
Cataract nuclear	17	24	33	1
Cataract operation	5	5	12	2
Cataract operation complication	0	1	0	0
Cataract subcapsular	36	51	71	3
Chalazion	2	0	0	0
Chorioretinal atrophy	0	1	0	0
Choroidal detachment	1	1	0	0
Choroidal dystrophy	0	0	1	0
Chromatopsia	5	4	0	0
Congenital eye naevus	0	2	0	0
Conjunctival cyst	0	0	1	0
Conjunctival disorder	0	0	1	0
Conjunctival haemorrhage	6	128	163	5
Conjunctival hyperaemia	1	6	2	0
Conjunctival irritation	0	1	0	0
Conjunctival oedema	1	1	4	0
Conjunctivitis	2	1	0	0
Conjunctivitis allergic	0	4	1	0

Adverse Event	Laser (N=330)	IVT 1mg (N =256)	IVT 4mg (N =254)	Nonstudy Eye Injected with Study Drug (N =22)
Conjunctivitis bacterial	1	0	2	0
Conjunctivitis viral	0	0	1	0
Corneal abrasion	7	2	2	0
Corneal defect	0	0	1	0
Corneal deposits	1	0	0	1
Corneal disorder	0	0	1	0
Corneal epithelium defect	0	0	1	0
Corneal erosion	0	1	0	0
Corneal oedema	0	2	2	0
Corneal opacity	2	1	4	0
Corneal pigmentation	1	0	0	0
Corneal scar	0	0	1	0
Corneal striae	0	1	0	0
Cutis laxa	0	3	2	0
Dandruff	1	0	1	0
Descemet's membrane disorder	0	1	0	0
Detachment of retinal pigment epithelium	0	0	1	0
Diplopia	3	0	3	3
Discomfort	0	1	0	0
Dry eye	6	7	5	0
Dry skin	0	1	0	0
Ecchymosis	0	1	0	0
Erythema	0	7	1	0
Erythema of eyelid	1	1	0	0
Eye burns	1	0	0	0
Eye discharge	1	3	4	1
Eye disorder	1	2	2	0
Eye infection viral	0	0	1	0
Eye inflammation	0	0	2	0
Eye injury	0	0	1	0
Eye irritation	1	9	12	0
Eye laser surgery	0	0	1	0
Eye pain	8	25	37	0
Eye pruritus	6	16	9	1
Eye redness	0	2	0	0
Eye swelling	1	0	2	0
Eyelid disorder	1	0	1	0
Eyelid function disorder	0	0	1	0

Adverse Event	Laser (N=330)	IVT 1mg (N =256)	IVT 4mg (N =254)	Nonstudy Eye Injected with Study Drug (N =22)
Eyelid infection	1	0	0	0
Eyelid irritation	0	1	0	0
Eyelid margin crusting	2	1	4	0
Eyelid oedema	2	4	6	0
Eyelid ptosis	4	1	9	0
Facial pain	0	0	1	0
Flat anterior chamber of eye	0	0	1	0
Foreign body in eye	5	50	44	1
Foreign body sensation in eyes	3	3	4	0
Foreign body trauma	0	0	1	0
Glaucoma	0	0	3	0
Gliosis	0	2	0	0
Growth of eyelashes	0	0	0	1
Guttate psoriasis	0	0	1	0
Headache	1	0	4	0
Hyalosis asteroid	0	3	0	0
Hyperaemia	0	0	1	0
Hypersensitivity	0	0	1	0
Hyphaema	0	2	2	0
Hypoaesthesia	0	0	0	1
Impaired driving ability	0	1	0	0
Injection site discomfort	0	1	1	0
Injection site erythema	0	0	2	0
Injection site haemorrhage	0	2	11	0
Injection site irritation	0	1	2	0
Injection site pain	0	1	1	0
Injection site pruritus	0	0	1	0
Injection site swelling	0	2	0	0
Intraocular pressure increased	16	59	143	9
Intraocular pressure test abnormal	0	0	1	0
Iris adhesions	1	0	1	0
Iris vascular disorder	2	3	1	0
Iritis	2	2	4	0
Keratitis	1	0	2	0
Keratitis sclerosing	0	1	0	0
Keratoconjunctivitis sicca	1	0	2	0
Keratopathy	2	0	0	0
Lacrimation increased	10	23	14	0
Lenticular opacities	1	1	3	0
Lenticular pigmentation	0	0	1	0

Adverse Event	Laser (N=330)	IVT 1mg (N=256)	IVT 4mg (N=254)	Nonstudy Eye Injected with Study Drug (N=22)
Ligament injury	0	1	0	0
Macular cyst	1	0	0	0
Macular hole	0	2	1	0
Medication residue	0	5	12	1
Nausea	1	0	0	0
Ocular discomfort	0	4	2	0
Ocular hyperaemia	0	3	7	0
Ocular hypertension	0	0	1	0
Optic atrophy	2	4	1	0
Optic ischaemic neuropathy	0	1	0	0
Optic nerve cup/disc ratio increased	0	0	2	0
Optic nerve cupping	1	1	0	0
Optic nerve disorder	0	2	0	0
Orbit atrophy	0	1	0	0
Pain	2	8	3	0
Papilloedema	1	0	0	0
Paracentesis	0	1	0	0
Periorbital haematoma	0	0	3	0
Peripheral vascular disorder	1	0	0	0
Photophobia	2	5	3	0
Photopsia	5	3	3	0
Photosensitivity reaction	0	2	0	0
Posterior capsule opacification	2	2	6	0
Procedural pain	1	0	1	0
Pruritus	0	4	3	0
Punctate keratitis	3	5	9	0
Pupillary disorder	0	0	0	1
Red blood cell abnormality	0	1	0	0
Retinal artery embolism	1	0	0	0

Source: Allergan Table 2.7.4.7-DME 2.03Summary of Study Eye Ocular Adverse Events Coded As of 10/01/07

9633 SCORE Ocular Adverse Events

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ON ORIGINAL

MedDRA term	Treatment Group					
	1mg (N=196)		4mg (N=200)		ISC (N=198)	
	Nbr Patients	Pct Incidence	Nbr Patients	Pct Incidence	Nbr Patients	Pct Incidence
Abnormal sensation in eye	3	1.5	4	2.0	3	1.5
Accommodation disorder	1	0.5	2	1.0	1	0.5
Altered visual depth perception	1	0.5	1	0.5	0	0
Angle closure glaucoma	0	0	1	0.5	0	0
Anterior chamber cell	0	0	5	2.5	0	0
Anterior chamber flare	1	0.5	1	0.5	0	0
Asthenopia	1	0.5	0	0	0	0
Blepharal papilloma	0	0	1	0.5	0	0
Blepharitis	3	1.5	3	1.5	2	1.0
Blepharospasm	2	1.0	0	0	2	1.0
Burning sensation	0	0	1	0.5	0	0
Cataract	4	2.0	24	12.0	4	2.0
Cataract cortical	0	0	2	1.0	0	0
Cataract nuclear	3	1.5	2	1.0	1	0.5
Cataract operation	1	0.5	7	3.5	0	0
Cataract subcapsular	2	1.0	10	5.0	0	0
Chalazion	0	0	1	0.5	0	0
Conjunctival disorder	1	0.5	0	0	0	0
Conjunctival haemorrhage	29	14.8	35	17.5	2	1.0
Conjunctival hyperaemia	1	0.5	1	0.5	0	0
Conjunctival oedema	1	0.5	1	0.5	0	0
Conjunctivitis	2	1.0	0	0	1	0.5
Conjunctivitis allergic	1	0.5	0	0	1	0.5
Conjunctivitis viral	0	0	1	0.5	0	0
Corneal abrasion	0	0	1	0.5	0	0
Corneal opacity	0	0	1	0.5	0	0
Dandruff	0	0	0	0	1	0.5
Diplopia	1	0.5	1	0.5	0	0
Discomfort	1	0.5	1	0.5	0	0
Drug hypersensitivity	0	0	1	0.5	0	0
Dry eye	2	1.0	1	0.5	4	2.0
Dry eye NOS	1	0.5	0	0	0	0
Endophthalmitis	0	0	2	1.0	0	0
Episcleritis	1	0.5	0	0	0	0
Erythema	0	0	1	0.5	0	0
Eye degenerative disorder	1	0.5	0	0	0	0
Eye discharge	1	0.5	0	0	0	0
Eye injury	0	0	2	1.0	0	0
Eye irritation	13	6.6	12	6.0	2	1.0
Eye pain	16	8.2	11	5.5	3	1.5
Eye pruritus	2	1.0	2	1.0	0	0
Eye redness	0	0	0	0	1	0.5
Eyelid disorder	0	0	1	0.5	0	0
Eyelid irritation	0	0	1	0.5	0	0

MedDRA term	Treatment Group					
	1 mg (N=196)		4 mg (N=200)		SC (N=198)	
	Nb. Patients	Pct. Incidence	Nb. Patients	Pct. Incidence	Nb. Patients	Pct. Incidence
Eyelid margin crusting	0	0	1	0.5	0	0
Eyelid oedema	1	0.5	1	0.5	1	0.5
Eyelid ptosis	0	0	3	1.5	0	0
Foreign body in eye	51	26.0	32	16.0	2	1.0
Foreign body sensation in eyes	0	0	2	1.0	0	0
Foreign body trauma	1	0.5	0	0	0	0
Glare	1	0.5	1	0.5	0	0
Glaucoma	3	1.5	4	2.0	1	0.5
Haemorrhage	0	0	0	0	1	0.5
Headache	1	0.5	0	0	2	1.0
Hordeolum	2	1.0	1	0.5	0	0
Hypersensitivity	0	0	0	0	1	0.5
Hyphaema	2	1.0	0	0	0	0
Injection site irritation	1	0.5	0	0	0	0
Injection site pain	2	1.0	0	0	0	0
Intraocular pressure increased	21	10.7	59	29.5	3	1.5
Iridocyclitis	1	0.5	0	0	0	0
Iris disorder	2	1.0	1	0.5	0	0
Iris vascular disorder	0	0	1	0.5	0	0
Iritis	1	0.5	0	0	0	0
Lacrimation increased	2	1.0	3	1.5	3	1.5
Macular hole	0	0	1	0.5	0	0
Macular ischaemia	0	0	0	0	1	0.5
Medication residue	0	0	7	3.5	0	0
Metamorphopsia	0	0	1	0.5	0	0
Ocular discomfort	2	1.0	1	0.5	0	0
Ocular hyperaemia	1	0.5	1	0.5	0	0
Optic nerve cup/disc ratio increased	1	0.5	0	0	0	0
Optic neuritis	0	0	0	0	1	0.5
Papilloedema	0	0	0	0	1	0.5
Papilloma	1	0.5	0	0	0	0
Photophobia	1	0.5	1	0.5	0	0
Photopsia	2	1.0	2	1.0	0	0
Pinguecula	1	0.5	2	1.0	0	0
Posterior capsule opacification	1	0.5	1	0.5	0	0
Pruritus	1	0.5	0	0	0	0
Pterygium	0	0	1	0.5	0	0
Punctate keratitis	1	0.5	0	0	0	0
Pupillary reflex impaired	0	0	1	0.5	0	0
Retinal pigment epitheliopathy	1	0.5	0	0	0	0
Retinal vasculitis	1	0.5	0	0	0	0
Scotoma	1	0.5	0	0	2	1.0
Tenderness	1	0.5	1	0.5	0	0
Vitreous detachment	4	2.0	6	3.0	1	0.5
Vitreous floaters	41	20.9	52	26.0	3	1.5
Vitreous opacities	0	0	2	1.0	0	0

Source: Allergan Table 2.7.4.7-SCORE 2.04 Ocular Adverse Events Summary – Study Eye

7.4.2 Laboratory Findings

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.4.3 Vital Signs

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.4.4 Electrocardiograms (ECGs)

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.4.5 Special Safety Studies

See Section 7.3.1 Submission Specific Primary Safety Concerns.

7.4.6 Immunogenicity

Not applicable. Drug product is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.5.2 Time Dependency for Adverse Events

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

7.5.3 Drug-Demographic Interactions

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

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.

7.5.4 Drug-Disease Interactions

There are a number of known disease interactions with systemic corticosteroids; the class labeling includes these interactions: alterations in endocrine function, increased risks related to infections, alterations in cardiovascular/renal function, increased risk of gastrointestinal perforation in patients with certain GI disorders, ophthalmic effects, behavioral and mood disturbances, decrease in bone density, and neuromuscular effects

See Section 2.4 of this review for a more complete listing.

7.5.5 Drug-Drug Interactions

There are a number of known drug interactions with systemic corticosteroids; the class labeling includes these interactions. b(4)

1. Anticoagulant agents: May enhance or diminish anticoagulant effects
2. Antidiabetic agents: May increase blood glucose concentrations.
3. CYP 3A4 inducers and inhibitors: May respectively increase or decrease clearance of corticosteroids necessitating dose adjustment
4. NSAIDS including aspirin and salicylates: Increased risk of gastrointestinal side effects.

See the attached revised labeling for a more complete listing.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were performed by the applicant.

7.6.2 Human Reproduction and Pregnancy Data

Per the corticosteroid class labeling for this product: Prednisolone can cause fetal harm when administered to a pregnant woman. Human and animal studies suggest that use of corticosteroids during the first trimester of pregnancy is associated with an increased risk of orofacial clefts, intrauterine growth restriction and decreased birth weight. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

7.6.3 Pediatrics and 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.

Long-term use of corticosteroids can have negative effects on growth and development in children.

Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully monitored.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

7.7 Additional Submissions

8 Postmarketing Experience

There is over a 50 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.

The safety and efficacy of Trivaris administration by the intradermal, intra-articular, and intrabursal routes is established in KENALOG-40 (triamcinolone acetonide injectable suspension) NDA 14-901 and is described in the package insert.

9 Appendices

9.1 Literature Review/References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

9.2 Advisory Committee Meeting

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

9.3 Labeling Recommendations

15 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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