

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-048/22-223

MEDICAL REVIEW

Medical Officer's Review of NDA 22-048 / 22-223
Review #2

NDA 22-048 / 22-223

Medical Officer's Review #2

Submission Date: November 28, 2007
Review Completed: November 29, 2007

(Proposed) Trade Name:

TRIESENCE™

Established Name:

triamcinolone acetonide injectable suspension 40 mg/mL

Applicant:

Alcon Research, Inc
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 293-0450

Reviewer's Comments:

Revised labeling based on previous review, discussion with the applicant, and a corrected package insert transmitted by the applicant on November 28, 2007.

The applicant has accepted all changes to the labeling as requested by the Division. This labeling is acceptable.

**Appears This Way
On Original**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRIESENCE™ safely and effectively. See full prescribing information for TRIESENCE™.

**TRIESENCE™ (triamcinolone acetonide injectable suspension)
40 mg/mL**

Initial U.S. Approval: 1957

INDICATIONS AND USAGE

TRIESENCE™ is a synthetic corticosteroid indicated for:

- Treatment of the following ophthalmic diseases: sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids. (1.1)
- Visualization during vitrectomy. (1.2)

DOSAGE AND ADMINISTRATION

- Initial recommended dose for all indications except visualization: 4 mg (100 microliters of 40 mg/mL suspension) with subsequent dosage as needed over the course of treatment. (2.1)
- Recommended dose for visualization: 1 to 4 mg (25 to 100 microliters of 40 mg/mL suspension) administered intravitreally. (2.2)

DOSAGE FORMS AND STRENGTHS

Single use 1 mL vial containing 40 mg/mL of triamcinolone acetonide suspension. (3)

CONTRAINDICATIONS

- Patients with systemic fungal infections. (4)
- Hypersensitivity to triamcinolone or any component of this product. (4)

WARNINGS AND PRECAUTIONS

- TRIESENCE™ is a suspension; it should not be administered intravenously. (5.1)
- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure. (5.1)

- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and hyperglycemia: Monitor patients for these conditions and taper doses gradually. (5.2)
- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection. (5.3)
- Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, potassium serum levels. (5.4)
- GI perforation: Increased risk in patients with certain GI disorders. (5.5)
- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. (5.6)
- Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy. (5.7)
- Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids. (5.8)
- Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy. (5.9)
- Use in pregnancy: Fetal harm can occur with first trimester use. (5.10)
- Weight gain: May cause increased appetite. (5.11)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Anticoagulant agents: May enhance or diminish anticoagulant effects. Monitor coagulation indices. (7)
- Antidiabetic agents: May increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required. (7)
- CYP 3A4 inducers and inhibitors: May respectively increase or decrease clearance of corticosteroids necessitating dose adjustment. (7)
- NSAIDs including aspirin and salicylates: Increased risk of gastrointestinal side effects. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November 2007

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1. Ophthalmic Diseases

TRIESENCE™ (triamcinolone acetonide injectable suspension) 40 mg/mL is indicated for:

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

1.2 Visualization during Vitrectomy

TRIESENCE™ is indicated for visualization during vitrectomy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Treatment of Ophthalmic Diseases

The initial recommended dose of TRIESENCE™ is 4 mg (100 microliters of 40 mg/mL suspension) with subsequent dosage as needed over the course of treatment.

2.2 Dosage for Visualization during Vitrectomy

The recommended dose of TRIESENCE™ is 1 to 4 mg (25 to 100 microliters of 40 mg/mL suspension) administered intravitreally.

2.3 Preparation for Administration

STRICT ASEPTIC TECHNIQUE IS MANDATORY. The vial should be vigorously shaken for 10 seconds before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. After withdrawal, TRIESENCE™ should be injected without delay to prevent settling in the syringe. Careful technique should be employed to avoid the possibility of entering a blood vessel or introducing organisms that can cause infection.

2.4 Administration

The injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

Following the injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before TRIESENCE™ is administered to the other eye.

3 DOSAGE FORMS AND STRENGTHS

Single use 1 mL vial containing 40 mg/mL of sterile triamcinolone acetonide suspension.

4 CONTRAINDICATIONS

Corticosteroids are contraindicated in patients with systemic fungal infections.

Triamcinolone is contraindicated in patients who are hypersensitive to corticosteroids or any components of this product. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy. [See *Adverse Reactions (6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Ophthalmic Effects

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

Risk of infection

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Corticosteroids may enhance the establishment of secondary ocular infections due to fungi or viruses. If an infection occurs during corticosteroid therapy, it should be promptly controlled by suitable antimicrobial therapy. See also *Increased Risks Related to Infection (5.3)*.

Elevated Intraocular Pressure

Increases in intraocular pressure associated with triamcinolone acetonide injection have been observed in 20-60% of patients. This may lead to glaucoma with possible damage to the optic nerve. Effects on intraocular pressure may last up to 6 months following injection and are usually managed by topical glaucoma therapy. A small percentage of patients may require aggressive non-topical treatment. Intraocular pressure as well as perfusion of the optic nerve head should be monitored and managed appropriately.

Endophthalmitis

The rate of infectious culture positive endophthalmitis is 0.5%. Proper aseptic techniques should always be used when administering triamcinolone acetonide. In addition, patients should be monitored following the injection to permit early treatment should an infection occur.

Cataracts

Use of corticosteroids may produce cataracts, particularly posterior subcapsular cataracts.

Patients with Ocular Herpes Simplex

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.

5.2 Alterations in Endocrine Function

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 reinstated.

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.

5.3 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 corticosteroids 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 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.

5.4 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.

5.5 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.

5.6 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.

5.7 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.

5.8 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.

5.9 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.

5.10 Use in Pregnancy

Triamcinolone acetonide 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. [*See Use in Specific Populations (8.1)*].

5.11 Weight Gain

Systemically administered corticosteroids may increase appetite and cause weight gain.

5.12 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.

5.13 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.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse event data were collected from 300 published articles containing data from controlled and uncontrolled clinical trials which evaluated over 14,000 eyes treated with different concentrations of triamcinolone acetonide. The most common dose administered within these trials was triamcinolone acetonide 4 mg administered as primary or adjunctive therapy primarily as a single injection.

The most common reported adverse events following administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.

Less common reactions occurring in up to 2% include endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, and detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

Common adverse reactions for systemically administered corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

Other reactions reported to have occurred with the administration of corticosteroids include:

Allergic Reactions: Anaphylactoid reaction, anaphylaxis, angioedema

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scalp, edema, facial erythema, hyper or hypo-pigmentation, impaired wound healing, increased sweating, petechiae and ecchymoses, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria

Endocrine: Abnormal fat deposits, decreased carbohydrate tolerance, development of Cushingoid state, hirsutism, manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycemic agents in diabetics, menstrual irregularities, moon facies, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness), suppression of growth in children

Fluid and Electrolyte Disturbances: Potassium loss, hypokalemic alkalosis, sodium retention

Gastrointestinal: Abdominal distention, elevation in serum liver enzymes levels (usually reversible upon discontinuation), hepatomegaly, hiccups, malaise, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, ulcerative esophagitis

Metabolic: Negative nitrogen balance due to protein catabolism

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures

Neurological: Arachnoiditis, convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually following discontinuation of treatment, insomnia, meningitis, neuritis, neuropathy, paraparesis/paraplegia, paresthesia, sensory disturbances, vertigo

Reproductive: Alteration in motility and number of spermatozoa.

7 DRUG INTERACTIONS

- **Amphotericin B:** There have been cases reported in which concomitant use of Amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure. *See Potassium depleting agents.*
- **Anticholinesterase agents:** Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.
- **Anticoagulant agents:** Co-administration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.
- **Antidiabetic agents:** Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
- **Antitubercular drugs:** Serum concentrations of isoniazid may be decreased.
- **CYP 3A4 inducers (e.g. barbiturates, phenytoin, carbamazepine, and rifampin):** Drugs such as barbiturates, phenytoin, ephedrine, and rifampin, which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of corticosteroid and require that the dosage of corticosteroid be increased.

- **CYP 3A4 inhibitors (e.g., ketoconazole, macrolide antibiotics):** Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60% leading to an increased risk of corticosteroid side effects.
- **Cholestyramine:** Cholestyramine may increase the clearance of corticosteroids.
- **Cyclosporine:** Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use.
- **Digitalis:** Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.
- **Estrogens, including oral contraceptives:** Estrogens may decrease the hepatic metabolism of certain corticosteroids thereby increasing their effect.
- **NSAIDs including aspirin and salicylates:** Concomitant use of aspirin or other non-steroidal antiinflammatory agents and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.
- **Potassium depleting agents (e.g., diuretics, Amphotericin B):** When corticosteroids are administered concomitantly with potassium-depleting agents, patients should be observed closely for development of hypokalemia.
- **Skin tests:** Corticosteroids may suppress reactions to skin tests.
- **Toxoids and live or inactivated vaccines:** Due to inhibition of antibody response, patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D [*See Warnings and Precautions (5.10)*]

Multiple cohort and case controlled studies in humans suggest that maternal corticosteroid use during the first trimester increases the rate of cleft lip with or without cleft palate from about 1/1000 infants to 3- 5/1000 infants. Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero.

Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. In rats and rabbits, triamcinolone acetonide was teratogenic at inhalation doses of 0.02 mg/kg and above and in monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 0.5 mg/kg (1/4 and 7 times the recommended human dose). Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in monkeys were cranial malformations. These effects are similar to those noted with other corticosteroids.

Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

8.3 Nursing Mothers

Corticosteroids are secreted in human milk. Reports suggest that steroid concentrations in human milk are 5 to 25% of maternal serum levels, and that total infant daily doses are small, less than 0.2% of the maternal daily dose. The risk of infant exposure to steroids through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

8.4 Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well established course of effect of corticosteroids which is similar in pediatric and adult populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults. [See *Adverse Reactions (6)*].

Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Children, who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The linear growth of children treated with corticosteroids by any route should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of other treatment alternatives. In order to minimize the potential growth effects of corticosteroids, children should be titrated to the lowest effective dose.

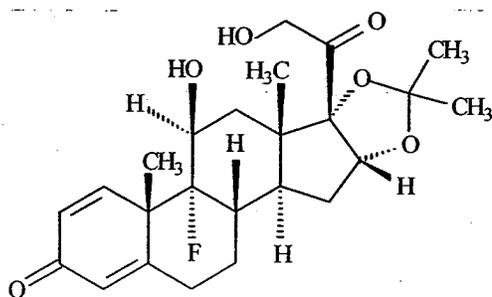
8.5 Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience with triamcinolone has not identified differences in responses between the elderly and younger patients. However, the incidence of corticosteroid-induced side effects may be increased in geriatric patients and are dose-related. Osteoporosis is the most frequently encountered complication, which occurs at a higher incidence rate in corticosteroid-treated geriatric patients as compared to younger populations and in age-matched controls. Losses of bone mineral density appear to be greatest early on in the course of treatment and may recover over time after steroid withdrawal or use of lower doses.

11 DESCRIPTION

TRIESENCE™ (triamcinolone acetonide injectable suspension) is a synthetic corticosteroid with anti-inflammatory action. Each mL of the sterile, aqueous suspension provides 40 mg of triamcinolone acetonide, with sodium chloride for isotonicity, 0.5% (w/v) carboxymethylcellulose sodium and 0.015% polysorbate 80. It also contains potassium chloride, calcium chloride (dihydrate), magnesium chloride (hexahydrate), sodium acetate (trihydrate), sodium citrate (dihydrate) and water for injection. Sodium hydroxide and hydrochloric acid may be present to adjust pH to a target value 6 – 7.5.

The chemical name for triamcinolone acetonide is 9-Fluro- 11β, 16α, 17,21-tetrahydroxypregna- 1,4-diene- 3,20-dione cyclic 16,17- acetal with acetone. Its structural formula of C₂₄H₃₁FO₆ is:



434.50 MW

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Triamcinolone acetonide possesses glucocorticoid activity typical of this class of drug, but with little or no mineralocorticoid activity. For the purposes of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Prednisone, 5	Paramethasone, 2
Hydrocortisone, 20	Methylprednisolone, 4	Betamethasone, 0.75
Prednisolone, 5	Triamcinolone, 4	Dexamethasone, 0.75

Corticosteroids have been demonstrated to depress the production of eosinophils and lymphocytes, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited.

12.2 Pharmacokinetics

Aqueous humor pharmacokinetics of triamcinolone have been 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 ranged from 2151 to 7202 ng/mL, half-life 76 to 635 hours, and the area under the concentration-time curve (AUC_{0-t}) from 231 to 1911 ng.h/mL following the single intravitreal administration. 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 from the vitreous was much faster (3.2 days) relative to patients that had not undergone vitrectomy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of mutagenicity was detected from *in-vitro* tests conducted with triamcinolone acetonide including a reverse mutation test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells. With regard to carcinogenicity, in a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 0.001 mg/kg and in a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 0.003 mg/kg (less than 1/25th of the recommended human dose). In male and female rats, triamcinolone acetonide caused no change in pregnancy rate at oral doses up to 0.015 mg/kg, but caused increased fetal resorptions and stillbirths and decreases in pup weight and survival at doses of 0.005 mg/kg (less than 1/10th of the recommended human dose).

13.2 Animal Toxicology and/or Pharmacology

Studies were conducted with triamcinolone acetonide, including those employing the proposed dosage form, i.e., 4.0% triamcinolone acetonide injectable suspension formulation containing 0.5% carboxymethylcellulose and 0.015% polysorbate-80 in a balanced salt solution. Triamcinolone acetonide was demonstrated to be non-inflammatory when injected intravitreally in NZW rabbits, non-cytotoxic to mouse L-929 cells in an *in-vitro* assay and non-sensitizing in a guinea-pig maximization assay. Furthermore, the results of single-dose intravitreal injection studies with triamcinolone acetonide in both rabbits and monkeys demonstrate that the drug is well tolerated for up to one month with only minor findings of slight decrease in body weight gain and slight corneal thinning.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRIESENCE™ (triamcinolone acetonide injectable suspension) is supplied as 1 mL of a 40 mg/mL sterile triamcinolone acetonide suspension in a flint Type 1 single use glass vial with a gray rubber stopper and a natural flip-off seal. Each labeled vial is sealed in a polycarbonate blister with a backing material which provides tamper evidence and is stored in a carton.

- 1 mL single use vial (NDC 0065-0543-01)

Storage

Store at 4° - 25° C (39° - 77° F); Do Not Freeze. Protect from light by storing in carton.

17 PATIENT COUNSELING INFORMATION

Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.

There are a number of medicines that can interact with corticosteroids such as triamcinolone. Patients should inform their health-care provider of all the medicines they are taking, including over-the counter and prescription medicines (such as phenytoin, diuretics, digitalis or digoxin, rifampin, amphotericin B, cyclosporine, insulin or diabetes medicines, ketoconazole, estrogens including birth control pills and hormone replacement therapy, blood thinners such as warfarin, aspirin or other NSAIDS, barbiturates), dietary supplements, and herbal products. If patients are taking any of these drugs, alternate therapy, dosage adjustment, and/or special test may be needed during the treatment.

Patients should be advised of common adverse reactions that could occur with corticosteroid use to include elevated intraocular pressure, cataracts, fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

U.S. Patent No. 6,395,294

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Recommendations:

NDA 22-048 / 22-223 for Triesence (triamcinolone acetonide injectable suspension) 40 mg/mL is recommended for approval with the labeling revisions found in this review.

Martin P. Nevitt, M.D., M.P.H.
Medical Officer

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Clinical Review
Martin P. Nevitt, M.D., M.P.H.
NDA 22-048
Triesence (triamcinolone acetonide injectable suspension)

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

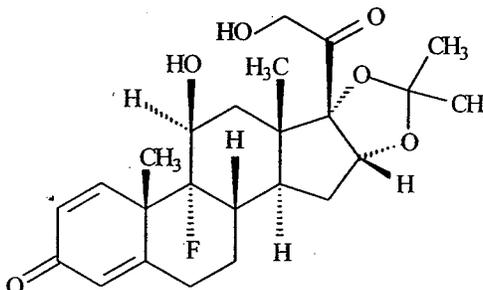
Reviewer Name Martin P. Nevitt, M.D., M.P.H.
Review Completion Date Oct. 24, 2007

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:

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.

Dosage for Visualization During Vitrectomy:

The recommended dose of TRIESENCE™ is 1 to 4 mg (25 µl to 100 µl of 40 mg/mL suspension) administered intravitreally.

(Proposed) Indication

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

(Proposed) Intended Population

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

_____, and, patients undergoing
vitrectomy for visualization of
vitreous _____

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NDA 22-048
Triesence (triamcinolone acetonide injectable suspension)

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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, _____ 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

Clinical Review
Martin P. Nevitt, M.D., M.P.H.
NDA 22-048
Triesence (triamcinolone acetonide injectable suspension)

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 _____ sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical steroids; _____; and for visualization of vitreous _____ 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 _____ 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 _____ to

_____ the visualization of the vitreous _____ during vitrectomy.

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 Triesence 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.

Clinical Review

Martin P. Nevitt, M.D., M.P.H.

NDA 22-048

Triescence (triamcinolone acetonide injectable suspension)

For visualization during vitrectomy the recommended dose of Triescence is 1 to — mg (100 µl to — 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.

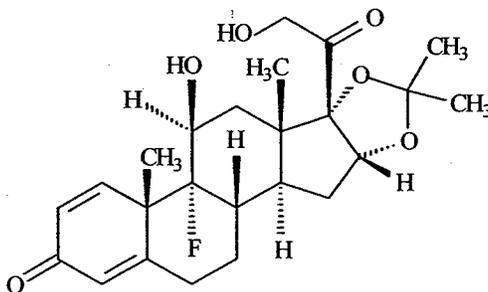
The efficacy and safety of corticosteroids in the pediatric population are based on the well-established use of triamcinolone acetonide.

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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



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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	0.55	_____	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 _____

_____ the visualization of the vitreous _____) 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) is a sterile, _____ 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 (_____ 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 _____ 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 _____

_____ the visualization of the vitreous during vitrectomy. For NDA 22-223 a 10 month review 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 _____. 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.

L

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 for for visualization 1 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 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	$-\log_{10}(\text{value})$
ETDRS Letters	$(85 - \text{value}) \times 0.02$
logMAR Units	value
Snellen: 20 /	$-\log_{10}(20/\text{value})$
Snellen: 6 /	$-\log_{10}(6/\text{value})$

* 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)

Clinical Review
Martin P. Nevitt, M.D., M.P.H.
NDA 22-048
Triesence (triamcinolone acetonide injectable suspension)

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**

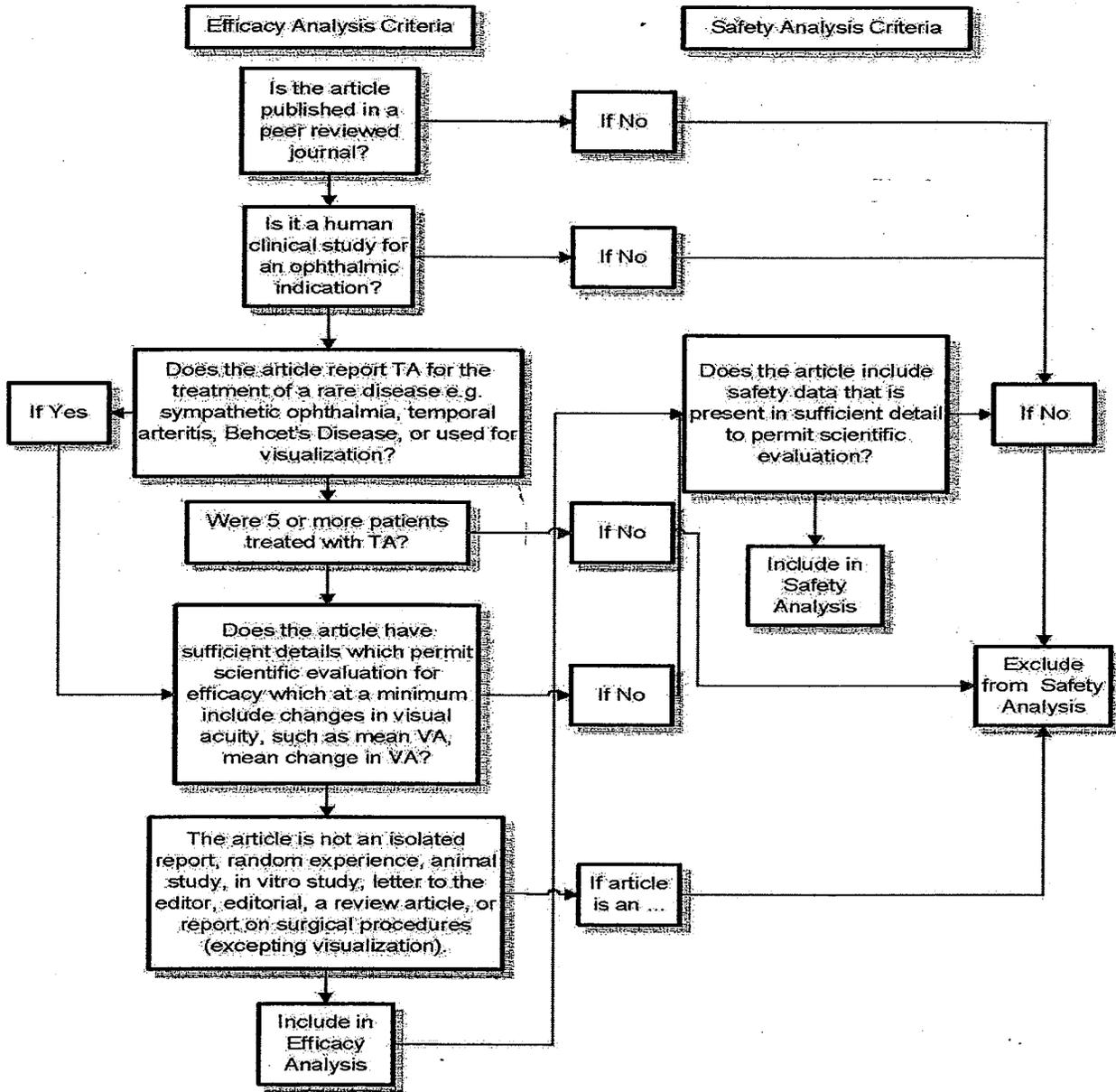
Inclusion / Exclusion Criteria

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.

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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, or 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,

Clinical Review

Martin P. Nevitt, M.D., M.P.H.

NDA 22-048

Triesence (triamcinolone acetonide injectable suspension)

- 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.

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 Triescence (triamcinolone acetonide injectable suspension)

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,†}	X ^B	X ^B
Anterior segment assessment		X ^{B,†}		
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	Intent –to-Treat (ITT)/Safety	Per Protocol (PP)
N=	N=	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 these 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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X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Visualization of the vitreous and _____ ring vitrectomy

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

	Articles	Total N	TA was safe and effective for visualization	
			N	%
All Reported Techniques Combined	33	3051	3040	99.6
Vitrectomy	19	2462	2461	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		"1"		"2"		"3"		Clearly Delineated "4"	
	"0"									
	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 juxtасcleral 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 \geq 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

SOC	Coded Event	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	
		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

SOC	Coded Event	5-<20 mg Triamcinolone + Adjunctive Therapy		≥ 20 mg Triamcinolone Primary Therapy		≥ 20 mg Triamcinolone + Adjunctive Therapy		Missing	
		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

SOC	Coded Event	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	
		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

SOC	Coded Event	5-<20 mg Triamcinolone + Adjunctive Therapy		≥ 20 mg Triamcinolone Primary Therapy		≥ 20 mg Triamcinolone + Adjunctive Therapy		Missing	
		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.

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

SOC	Coded Event	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	
		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.

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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

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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.

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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

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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.

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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
<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 safety 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, cited 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 Triesence 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 Triesence is 1 to 4 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, Triesence.

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.

Clinical Review
Martin P. Nevitt, M.D., M.P.H.
NDA 22-048
Triesence (triamcinolone acetonide injectable suspension)

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

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Clinical Review
Martin P. Nevitt, M.D., M.P.H.
NDA 22-048
Triesence (triamcinolone acetonide injectable suspension)

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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X § 552(b)(4) Draft Labeling

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