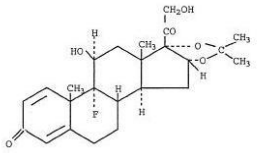
Submission Date: August 15, 2007
Review Date: June 16, 2008
Name: Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL

Therapeutic Class: Corticosteroid
Applicant: Allergan, Inc.

Structure $C_{24}H_{31}FO_6$ 

Indications:
Ophthalmic Use:

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

Intramuscular Use:

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

Intra-articular Use:

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

Background:

There is over a 50 year history of use of the active ingredient, triamcinolone acetonide, in the United States (marketed by Bristol-Myers, Squibb, Princeton, NJ, as KENALOG-40) with adequate demonstration of safety and efficacy for a variety of indications.

The safety and efficacy of Trivaris is supported by the Agency's findings of safety and efficacy for KENALOG-40 (triamcinolone acetonide injectable suspension), NDA 14-901 included in the labeling of Kenalog, by studies performed by Allergan and by additional information in the published literature.

KENALOG-40 is a sterile aqueous suspension containing triamcinolone acetonide at a concentration of 40 mg/mL, benzyl alcohol at a concentration of 0.9% (w/v) as a preservative,

and excipients. The KENALOG-40 package insert contains warnings regarding the use of benzyl alcohol in pediatric patients.[1]

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

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

The safety issues seen with this drug product are class issues for systemically administered corticosteroids.

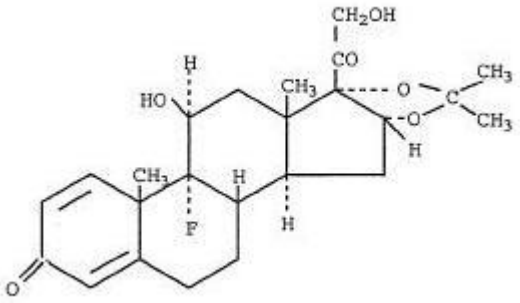
Product Information

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

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

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

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



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

Quantitative Composition for Trivaris

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

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

Safety Issues

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

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

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

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of

relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

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

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

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

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

Corticosteroids may exacerbate infections and increase risk of disseminated infection.

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

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

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

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

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

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

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

Corticosteroids should not be used in cerebral malaria.

Alterations in Cardiovascular/Renal Function
Corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. These agents should be used with caution in patients with hypertension, congestive heart failure, or renal insufficiency.

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

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

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

Ophthalmic Effects
Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

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

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

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

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

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

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

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

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

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

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

Neuromuscular Effects
Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the

ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

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

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

Submission Quality and Integrity

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

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

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

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

Compliance with Good Clinical Practices

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

Financial Disclosures

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

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

Chemistry Manufacturing and Controls

The Chemistry/Manufacturing Review was completed by Rao Kambhampati. There are no outstanding manufacturing issues.

Preclinical Pharmacology/Toxicology

The Pharm/Tox Review was completed by Zhou Chen. There are no outstanding pharmacology/toxicology issues beyond those known for the corticosteroid class of products.

Clinical Pharmacology

The Clinical Pharmacology Review was completed by Sarah Robertson. The application received a waiver of the requirement for submission of evidence of in vivo bioavailability.

Clinical

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

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

Summary and Conclusions:

NDA 22-220 supports the safety and effectiveness of Trivaris (triamcinolone acetonide injectable suspension) 80 mg/mL for:

1) Ophthalmic Use

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

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

2) Intramuscular Use

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

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

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

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

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

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

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

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

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

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

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

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

3) Intra-Articular Use

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

The safety and efficacy of Trivaris is supported by the Agency's findings of safety and efficacy for KENALOG-40 (triamcinolone acetonide injectable suspension), NDA 14-901 included in the labeling of Kenalog, by the studies performed by Allergan and submitted to this application and by additional information in the published literature.

The indications approved, along with the safety issues identified in the labeling are consistent with other triamcinolone acetonide injectable suspension applications approved for marketing with the exception of the warnings related to benzyl alcohol. This product does not include benzyl alcohol and therefore the labeling does not include risks related to benzyl alcohol.

There are no recommendations for additional postmarketing studies.

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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