CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

12-041/S038

Trade Name: Kenalog-10

Generic Name: Triamcinolone acetonide

Sponsor: Apothecon, Inc.

Approval Date: 6/16/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

12-041/S038

CONTENTS

Reviews / Information Included in this NDA Review.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 12-041/S-038
NDA 14-901/S-038

SUPPLEMENT APPROVAL

Bristol-Meyers Squibb
P. O. Box 4000
Princeton, NJ 08543-4000

Attention: Angela Glauberzon
Associate Director, Mature Products
Global Regulatory Sciences

Dear Ms. Glauberzon:

Please refer to your Supplemental New Drug Applications (sNDA) dated October 7, 2010, received October 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kenalog-10 (triamcinolone acetonide) Injection and Kenalog-40 (triamcinolone acetonide) Injection.

We acknowledge receipt of your amendment dated June 8, 2011.

These Changes Being Effected supplemental new drug applications propose revisions to the package insert to add information that Kenalog is not for epidural use and to add information to the Warning section that epidural use is not recommended. These supplements also provide for revisions to the Warnings-Neurologic and Adverse Reactions section of the products labels to include information regarding adverse events with epidural administration of corticosteroids.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Michelle Jordan, Regulatory Project Manager, at (301).

Sincerely,

{See appended electronic signature page}

Sally Seymour, M.D.
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
06/16/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

12-041/S038

LABELING

KENALOG®-10 INJECTION
triamcinolone acetonide injectable suspension, USP

NOT FOR USE IN NEONATES
CONTAINS BENZYL ALCOHOL

For Intra-articular or Intralesional Use Only

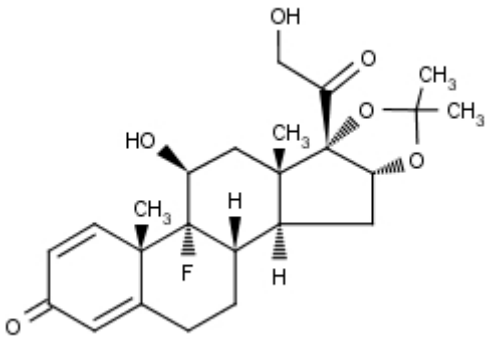
NOT FOR INTRAVENOUS, INTRAMUSCULAR, INTRAOCULAR, EPIDURAL, OR INTRATHECAL USE

DESCRIPTION

Kenalog®-10 Injection (triamcinolone acetonide injectable suspension, USP) is triamcinolone acetonide, a synthetic glucocorticoid corticosteroid with marked anti-inflammatory action, in a sterile aqueous suspension suitable for intralesional and intra-articular injection. THIS FORMULATION IS SUITABLE FOR INTRA-ARTICULAR AND INTRALESIONAL USE ONLY.

Each mL of the sterile aqueous suspension provides 10 mg triamcinolone acetonide, with sodium chloride for isotonicity, 0.9% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80; sodium hydroxide or hydrochloric acid may have been added to adjust pH between 5.0 and 7.5. At the time of manufacture, the air in the container is replaced by nitrogen.

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



MW 434.50

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

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

INDICATIONS AND USAGE

The intra-articular or soft tissue administration of Kenalog-10 Injection (triamcinolone acetonide injectable suspension, USP) 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, or osteoarthritis.

The intralesional administration of Kenalog-10 Injection is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabeticorum. Kenalog-10 Injection may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Kenalog-10 Injection is contraindicated in patients who are hypersensitive to any components of this product (see **WARNINGS: General**).

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

WARNINGS

General

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS: Pediatric Use**).

Because Kenalog-10 Injection (triamcinolone acetonide injectable suspension, USP) is a suspension, it should *not* be administered intravenously. Strict aseptic technique is mandatory.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**). Cases of serious anaphylactic reactions and anaphylactic shock, including death, have been reported in individuals receiving triamcinolone acetonide injection, regardless of the route of administration.

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Kenalog-10 Injection is a long-acting preparation, and is *not* suitable for use in acute stress situations.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an intravenous corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including Kenalog-10 Injection, should not be used for the treatment of traumatic brain injury.

Cardio-Renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when they are used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

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

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

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.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

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. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS: Drug Interactions:** *Amphotericin B injection and potassium-depleting agents*).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, or *Toxoplasma*.

It is recommended that latent amebiasis 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.

Similarly, 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 should not be used in cerebral malaria.

Tuberculosis

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.

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 cannot be predicted. Immunization

procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see **ADVERSE REACTIONS:** *Gastrointestinal* and *Neurologic/Psychiatric*).

Ophthalmic

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. 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. Corticosteroids should not be used in active ocular herpes simplex.

Adequate studies to demonstrate the safety of Kenalog Injection use by intraturbinal, subconjunctival, sub-Tenons, retrobulbar, and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased intraocular pressure, and visual disturbances including vision loss have been reported with intravitreal administration. Administration of Kenalog Injection intraocularly or into the nasal turbinates is not recommended.

Intraocular injection of corticosteroid formulations containing benzyl alcohol, such as Kenalog Injection, is not recommended because of potential toxicity from the benzyl alcohol.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

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.

Cardio-Renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

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.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Intra-Articular and Soft Tissue Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see **ADVERSE REACTIONS:** *Musculoskeletal*).

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (ie, 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 pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (ie, postmenopausal women) before initiating corticosteroid therapy.

Neuro-Psychiatric

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. (See **DOSAGE AND ADMINISTRATION**.)

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

Psychiatric derangements may appear when corticosteroids are used, 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.

Ophthalmic

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

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (ie, amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases: 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.

Anticoagulants, oral: Coadministration 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.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

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 this concurrent use.

Digitalis glycosides: 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.

Hepatic enzyme inducers (eg, barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory drugs) 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.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections: Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the

offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use

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

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. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, eg, severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). 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. Pediatric patients 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 (ie, cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

(listed alphabetically under each subsection)

The following adverse reactions may be associated with corticosteroid therapy:

Allergic reactions: Anaphylactoid reaction, anaphylaxis including anaphylactic reactions and anaphylactic shock, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial

infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, lupus erythematosus-like lesions, purpura, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration [see **WARNINGS: Neurologic**]), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, post injection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration.

Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration of corticosteroids (see **WARNINGS: Neurologic**).

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

General

NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS).

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in 3 or 4 divided doses (3.2 to 48 mg/m^2bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

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

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Intra-Articular Administration

Dosage

The initial dose of Kenalog-10 Injection for intra-articular administration may vary from 2.5 mg to 5 mg for smaller joints and from 5 mg to 15 mg for larger joints, depending on the specific disease entity being treated. Single injections into several joints, up to a total of 20 mg or more, have been given.

Intralesional

For intralesional administration, the initial dose per injection site will vary depending on the specific disease entity and lesion being treated. The site of injection and volume of injection should be carefully considered due to the potential for cutaneous atrophy.

Multiple sites separated by one centimeter or more may be injected, keeping in mind that the greater the *total* volume employed the more corticosteroid becomes available for systemic absorption and systemic effects. Such injections may be repeated, if necessary, at weekly or less frequent intervals.

Localization of Doses

The lower dosages in the initial dosage range of triamcinolone acetonide may produce the desired effect when the corticosteroid is administered to provide a localized concentration. The site and volume of the injection should be carefully considered when triamcinolone acetonide is administered for this purpose.

Administration

STRICT ASEPTIC TECHNIQUE IS MANDATORY. The vial should be shaken 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, inject without delay to prevent settling in the syringe.

Injection Technique

For treatment of joints, the usual intra-articular injection technique should be followed. If an excessive amount of synovial fluid is present in the joint, some, but not all, should be aspirated to aid in the relief of pain and to prevent undue dilution of the steroid.

With intra-articular administration, prior use of a local anesthetic may often be desirable. Care should be taken with this kind of injection, particularly in the deltoid region, to avoid injecting the suspension into the tissues surrounding the site, since this may lead to tissue atrophy.

In treating acute nonspecific tenosynovitis, care should be taken to ensure that the injection of Kenalog-10 Injection is made into the tendon sheath rather than the tendon substance. Epicondylitis may be treated by infiltrating the preparation into the area of greatest tenderness.

Intralesional

For treatment of dermal lesions, Kenalog-10 Injection should be injected directly into the lesion, ie, intradermally or subcutaneously. For accuracy of dosage measurement and ease of administration, it is preferable to employ a tuberculin syringe and a small-bore needle (23-25 gauge). Ethyl chloride spray may be used to alleviate the discomfort of the injection.

HOW SUPPLIED

Kenalog®-10 Injection (triamcinolone acetonide injectable suspension, USP) is supplied in 5 mL multiple-dose vials (NDC 0003-0494-20) providing 10 mg triamcinolone acetonide per mL.

Storage

Store at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
Product of Italy

1221154A5 Rev June 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

12-041/S038

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Division of Pulmonary, Allergy, and Rheumatology Products

Application #:	NDA 12041, 14901	**Application Type:**	IND
Sponsor:	Bristol Myers Squibb	**Proprietary Name:**	Kenalog-10, Kenalog-40
Investigator:		**USAN Name:**	triamcinalone
Category:	Gluocorticoids	**Route of Administration:**	Injection
Reviewer:	Sally Seymour, MD	**Review Date:**	June 15, 2011

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Submission Type	Comments
October 7, 2010	CBE Labeling Supplements	Kenalog 10 and 40
June 8, 2011	Amendment	Kenalog 10 and 40

REVIEW SUMMARY: This is a Medical Officer review of a CBE labeling supplement submitted by BMS for the Kenalog product labels. In this labeling supplement, BMS proposes to add information that Kenalog is "not for epidural use" and to add in the Warnings section that epidural use is not recommended. This SLR may be in response to the Division opening a Tracked Safety Issue (#822) for neurologic complications with epidural injection of corticosteroids, which was opened in November 2009.

The safety issues team (DPARP, DAAP, OSE) has been evaluating the safety issue of neurologic adverse reactions with epidural injection of corticosteroids. OSE completed a review on May 14, 2010 and noted reports of spinal cord infarction, paraplegia, quadriplegia, cortical blindness, stroke (including brainstem), and death following epidural administration of corticosteroids. Epidural administration of corticosteroids is an off-label use, but is a common procedure for the treatment of chronic pain. The SIT contemplated class labeling changes and a drug safety communication regarding this safety issue, but discussions with the Drug Safety Board raised concerns regarding this approach. Thus, the Safe Use group within the FDA was involved to enlist the key stakeholders regarding this safety issue.

Regarding the proposed labeling supplement, the Sponsor's proposed changes are acceptable. However, additional information regarding the types of events reported is recommended and the proposed edits are shown below (underline) for both the Kenalog and Kenalog 10 product labels.

Warnings - Neurologic

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of administration (see **ADVERSE REACTIONS:** *Gastrointestinal and Neurologic/Psychiatric*).

Adverse Reactions

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration (see **WARNINGS: Neurologic**).

These recommendations were conveyed to the Sponsor on May 11, 2011. IN a response dated June 8, 2011, the Sponsor accepted the agency's recommendations and included a couple minor clarifications highlighted below.

Warnings - Neurologic

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see **ADVERSE REACTIONS:** *Gastrointestinal* and *Neurologic/Psychiatric*).

Adverse Reactions

Neurologic/Psychiatric Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, ~~psychic~~psychiatric disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration of corticosteroids (see **WARNINGS: Neurologic**).

The proposed labeling additions are acceptable. The labeling supplements are recommended for approval.

OUTSTANDING ISSUES: None – recommendation for approval

RECOMMENDED REGULATORY ACTION:

Medical Reviewer: Sally Seymour, MD

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/s/

SALLY M SEYMOUR
06/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

12-041/S038

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 11, 2011

To: Angela Glauberzon	**From:** Ladan Jafari
Company: Bristol-Myers Squibb	Division of Pulmonary, Allergy and Rheumatology Products
FAX number: 609-252-6396	**Fax number:** 301-796-9728
Phone number: 609-252-5163	**Phone number:** 301-796-1231

Subject: Kenalog

Total Number of Pages Including Cover: 3

Comments: Labeling comments

Document to be mailed: YES ☑ NO

NDA 12041/S-38
NDA 14901/S-38

Dear Ms. Glauberzon:

We are reviewing your supplemental new drug applications dated October 7, 2010, which provided for revisions to the labeling for Kenalog 10 and Kenalog 40, to add information that Kenalog is "not for epidural use" and to add in the Warning section that epidural use is not recommended.

We request that you revise the labeling supplements incorporating our comments noted below (underline) and resubmit the labeling for these products by the close of business on May 20, 2011. Please note that we may have additional comments regarding these submissions as we continue to review the labeling for these products.

Warnings
Neurologic
Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of administration (see **ADVERSE REACTIONS:** *Gastrointestinal and Neurologic/Psychiatric*).

Adverse Reactions
Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration (see **WARNINGS: Neurologic**).

I may be reached at 301-796-1231 for any questions.

_____
Ladan Jafari, Safety Regulatory Project Manager

Drafted by: LJ/5-10-11

Initialed by: Barnes/5-10-11
Seymour/5-10-11

Filename: Kenalog labeling comments.doc

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LADAN G JAFARI
05/11/2011

Bristol-Myers Squibb

P.O. Box 4000 Princeton, NJ 08543-4000
www.bms.com

EPIDURAL-INTRATHECAL LABELING CBE
CHANGE OF CORRESPONDENT

NDA 12-041
Kenalog®-10 Injection (triamcinolone acetonide injectable suspension, USP)
(Sequence 0001)

October 7, 2010

Robert Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products
Center for Drug Evaluation and Research
Document Control Room
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Rappaport,

Reference is made to our approved New Drug Application for NDA 12-041 Kenalog®-10 Injection (triamcinolone acetonide injectable suspension, USP).

The purpose of this supplement is to provide revisions to the labeling as described below:

- **General** -Insertion of "epidural or intrathecal" in the general note to the customer.

- **Warnings (Neurologic)** - addition of mandatory warnings text that epidural and intrathecal administration should not be used and that reports of serious medical events have been associated with epidural and intrathecal routes of administration; correction of severe to serious and insertion of "epidural".

- **Adverse Reactions (Gastrointestinal)** - addition of cross-reference to the Warnings: Neurologic section

We also wish to amend the noted NDA with the following information. Effective immediately, please direct all correspondence and inquiries for this NDA to:

Angela Glauberzon
Associate Director, Regulatory Strategy Mature Products
Bristol-Myers Squibb Research & Development
P.O. Box 4000 (Mail Stop: D22-09)
Princeton, NJ 08543-4000

The submission has been prepared following the eCTD structure specified in the FDA Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications". A description of this electronic submission, including electronic media information as suggested in the FDA Guidance cited above is provided in Attachment 1 to this cover letter.

If there are any questions concerning this submission, please contact the undersigned at (609) 252-5163 or by secure email at angela.glauberzon@bms.com [or FAX (609) 252-6396].

Sincerely,

Angela Glauberzon
Associate Director, Mature products
Global Regulatory Sciences

AG/RH/tmc

Electronic Media Information

NDA No. 12-041
Kenalog-10 Injection (triamcinolone acetonide injectable suspension, USP)

October 7, 2010

Epidural-Intrathecal Labeling CBE and Change in Correspondent

The archival copy of this submission is a fully compliant electronic dossier and is being provided in lieu of paper as per the current FDA Guidance. The media for this electronic submission has been prepared as follows. The total size of the electronic submission is approximately 2.47 MB and is being provided via the Electronic Submission Gateway to the Central Document Room. There are 22 files and 6 folders. The files have been checked for viruses using McAfee Virus Scan Software (Version 8.5i) and no viruses were detected.

If there are any questions or comments concerning the technical aspects of this submission, please contact Cynthia Piccirillo, Director, e-Regulatory Liaison, Global Dossier Management at (203) 677-7625 or by secure e-mail at Cynthia.Piccirillo@bms.com.