# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

# 11-664 / S-062

***Trade Name:*** Decadron

***Generic Name:*** (dexamethasone)

***Sponsor:*** Merck & CO.

***Approval Date:*** May 17, 2004

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 11-664 / S-062

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 11-664 / S-062

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-664/S-062

Merck & Co., Inc.
Attention: Kenneth A. Kramer
Manager
Regulatory Affairs-Domestic
BLA-20 P.O.Box 4
West Point, PA 19486

Dear Mr. Kramer:

Please refer to your supplemental new drug application dated August 26, 2003, received August 27, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decadron (dexamethasone) Tablets.

This supplemental new drug application provides for revisions to the **PRECAUTIONS** section of the labeling.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the submitted labeling with the minor editorial revision listed below:

Under **PRECAUTIONS, Drug Interactions**, *Hepatic Enzyme Inducers* subsection, "Co-administration" is misspelled.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert submitted August 26 2003). These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 11-664/S-062." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Stacey Welch, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V

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

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/s/

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Sharon Hertz
5/17/04 04:30:34 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 11-664 / S-062

# APPROVED LABELING

7921151

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

TABLETS

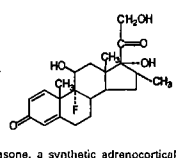
# DECADRON®

## (DEXAMETHASONE TABLETS, USP)

### DESCRIPTION

DECADRON* (dexamethasone tablets, USP) tablets, for oral administration, are supplied in two potencies, 0.5 mg and 0.75 mg. Inactive ingredients are calcium phosphate, lactose, magnesium stearate, and starch. Tablets DECADRON 0.5 mg also contain D&C Yellow 10 and FD&C Yellow 6. Tablets DECADRON 0.75 mg also contain FD&C Blue 1.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water.

### CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

### INDICATIONS AND USAGE

*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, and serum sickness.

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

*Endocrine disorders:* Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; may be used in conjunction with synthetic mineralocorticoid analogs where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, and 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, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.

*Miscellaneous:* Diagnostic testing of adrenocortical hyperfunction, 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.

*Ophthalmic diseases:* Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

*Renal diseases:* To induce a 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.

* Registered trademark of MERCK & CO., Inc.



### CONTRAINDICATIONS

Systemic fungal infections (see WARNINGS, *Fungal Infections*).

DECADRON tablets are contraindicated in patients who are hypersensitive to any components of this product.

### WARNINGS

*General*

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see ADVERSE REACTIONS).

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.

*Cardio-renal*

Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium. 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. 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. Adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and 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. If the patient is receiving steroids already, dosage may have to be increased.

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 life-threatening 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, 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 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*

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.

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, e.g., for Addison's disease.

*Viral Infections*

Chickenpox 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 chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

*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.

### PRECAUTIONS

*General*

The lowest possible dose of corticosteroids 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 corticosteroids 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 due to decreased metabolism of corticosteroids in patients with cirrhosis.

*Musculoskeletal*

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 pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (e.g., 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 (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 creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic 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.

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7921151 TABLETS **DECADRON®** (DEXAMETHASONE TABLETS, USP)

7921151
DECADRON* (Dexamethasone tablets, USP)

*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. As prolonged use may cause adrenal insufficiency and make patients dependent on corticosteroids, they should advise any medical attendants that they are taking corticosteroids and they should seek medical advice at once should they develop an acute illness including fever or other signs of infection. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including myalgia, arthralgia, and malaise.

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

*Drug Interactions*

*Aminoglutethimide:* Aminoglutethimide may diminish adrenal suppression by corticosteroids.

*Amphotericin B injection and potassium-depleting agents:* When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. In addition, 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 (see *Drug Interactions, Hepatic Enzyme Inducers, Inhibitors and Substrates*).

*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:* 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.

*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.

*Dexamethasone suppression test (DST):* False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

*Digitalis glycosides:* Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

*Ephedrine:* Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage.

*Estrogens, including oral contraceptives:* Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

*Hepatic Enzyme Inducers, Inhibitors and Substrates:* Drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity *(e.g., barbiturates, phenytoin, carbamazepine, rifampin)* may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 *(e.g., ketoconazole, macrolide antibiotics such as erythromycin)* have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP 3A4. Co-administration with other drugs that are metabolized by CYP 3A4 *(e.g., indinavir, erythromycin)* may increase their clearance, resulting in decreased plasma concentration.

*Ketoconazole:* Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to increased risk of corticosteroid side effects. In addition, ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal.

*Nonsteroidal anti-inflammatory agents (NSAIDS):* Concomitant use of aspirin (or other nonsteroidal anti-inflammatory 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.

*Phenytoin:* In post-marketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone co-administration, leading to alterations in seizure control.

*Skin tests:* Corticosteroids may suppress reactions to skin tests.

*Thalidomide:* Co-administration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

DECADRON* (Dexamethasone tablets, USP)

*Vaccines:* Patients on 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 substantial doses of 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. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

*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. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (patients >2 years of age), and aggressive lymphomas and leukemias (patients >1 month of age). Other indications for pediatric use of corticosteroids, e.g., 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 hypothalamic-pituitary-adrenal (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 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*

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.

### ADVERSE REACTIONS (listed alphabetically, under each subsection)

The following adverse reactions have been reported with DECADRON or other corticosteroids:

*Allergic reactions:* Anaphylactoid reaction, anaphylaxis, 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, *Cardio-renal*), edema, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

*Dermatologic:* Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

*Endocrine:* Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, 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, 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, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.

*Neurological/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.

*Ophthalmic:* Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

*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 overdosage is by supportive and symptomatic therapy. In the case of acute overdosage, according to the patient's condition, supportive therapy may include gastric lavage or emesis.

## DOSAGE AND ADMINISTRATION

*For oral administration*

The initial dosage varies from 0.75 to 9 mg a day depending on the disease being treated.

*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 that maintains 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 the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg of dexamethasone for a week followed by 4 to 12 mg every other day for one month have been shown to be effective (see PRECAUTIONS, *Neuro-psychiatric*).

In pediatric patients, the initial dose of dexamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02 to 0.3 mg/kg/day in three or four divided doses (0.6 to 9 mg/m²bsa/day).

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

| | |
|---|---|
| *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.*

*In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders,* the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone Sodium Phosphate injection, USP 4 mg per mL:
First Day
1 or 2 mL, intramuscularly
DECADRON tablets, 0.75 mg:
Second Day
4 tablets in two divided doses
Third Day
4 tablets in two divided doses
Fourth Day
2 tablets in two divided doses
Fifth Day
1 tablet
Sixth Day
1 tablet
Seventh Day
No treatment
Eighth Day
Follow-up visit

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

In *cerebral edema,* Dexamethasone Sodium Phosphate injection, USP is generally administered initially in a dosage of 10 mg intravenously followed by 4 mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with either Dexamethasone Sodium Phosphate injection, USP or DECADRON tablets in a dosage of 2 mg two or three times daily may be effective.

*Dexamethasone suppression tests*

1. Tests for Cushing's syndrome

Give 1.0 mg of DECADRON orally at 11:00 p.m. Blood is drawn for plasma cortisol determination at 8:00 a.m. the following morning.

For greater accuracy, give 0.5 mg of DECADRON orally every 6 hours for 48 hours. Twenty-four hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

2. Test to distinguish Cushing's syndrome due to pituitary ACTH excess from Cushing's syndrome due to other causes.

Give 2.0 mg of DECADRON orally every 6 hours for 48 hours. Twenty-four hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

## HOW SUPPLIED

Tablets DECADRON are compressed, pentagonal-shaped tablets, colored to distinguish potency. They are scored and coded on one side and embossed with DECADRON on the other. They are available as follows:

No. 7601 — 0.75 mg, bluish-green in color and coded MSD 63.
**NDC 0006-0063-12** 5-12 PAK® (package of 12)
**NDC 0006-0063-68** bottles of 100.
No. 7598 — 0.5 mg, yellow in color and coded MSD 41.
**NDC 0006-0041-68** bottles of 100.

*Storage*

Store at controlled room temperature 20 to 25°C (68 to 77°F).

Rx only

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued May 2004
Printed in USA

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 11-664 / S-062

# ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

## Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products
# REGULATORY HEALTH PROJECT MANAGER REVIEW

## Application/Material Reviewed

**Number:** NDA 11-664/SLR-062

**Drug:** Decadron® (dexamethasone tablets, USP) Tablets
0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg, and 6 mg

**Applicant:** Merck & Company, Inc. (Merck)

**Submission Date:** 26 August 2003

**Receipt Date:** 27 August 2003

## Background and Summary

Additional Supplemental New Drug Applications Pending Approval:

- S-046, dated 21 November 1986 and received 25 November 1986
- S-052, dated 18 July 1994 and received 21 July 1994
- S-054 (CBE), dated 26 March 1996 and received 29 March 1996 (package insert # 7921147)
- S-056 (CBE), dated 1 April 1997 and received 3 April 1997 (package insert # 7921148)
- S-059 (CBE), dated 24 July 2001 and received 25 July 2001 (package insert # 7921149)
- S-061 (CBE), dated 6 March 2002 and received 7 March 2002 (package insert # 7921150)

FDA sent Merck a 4 February 2001 Approvable letter in response to supplemental new drug applications S-046, S-052, S-054, and S-056. The letter proposed comprehensive revisions to the content and format of the product labeling. FDA also sent Merck a 17 January 2003 Not Approvable letter in response to "Special Supplement – Changes Being Effected" supplemental new drug applications S-059 and S-061, proposing changes to the **WARNINGS**, **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the labeling. Subsequently, Merck informed the FDA that S-059 and S-061 were submitted without addressing the revisions proposed in the 4 February 2001 Approvable letter because Merck has no record of receiving such a letter. FDA faxed the letter to Merck again on 28 January 2003 per the request of Mr. Kenneth Kramer of Merck. Merck agreed to respond to the 4 February 2001 Approvable letter, incorporate all outstanding supplements into the response, and incorporate a **Geriatric Use** subsection in the **PRECAUTIONS** section of the labeling.

This supplemental new drug application S-062 provides for labeling revisions in response to the 4 February 2001 Approvable letter, for revisions to maintain consistency with the 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets, and for revisions to the **PRECAUTIONS** section of the labeling to comply with the FDA Final Rule [21 CFR 201.57(f)(10)(ii)]. A new subsection, **Geriatric Use**, has been added to include information regarding the use of Decadron® Tablets in the elderly.

The submission is in electronic format and contains the following:

- Labeling history for Decadron® Tablets
- Last approved (25 August 1993) Decadron® Tablets labeling (S-050, package insert # 7420545)
- Current Decadron® Tablets labeling (package insert # 7921150)
- Proposed Decadron® Tablets labeling (package insert # 79211xx)
- Annotated Decadron® Tablets labeling (package insert # 79211xx)
- Supportive documentation (Reference 1, 2, and 3)

## Review (Proposed Changes and Reviewer Comment)

### DESCRIPTION

- Revised per FDA's 4 February 2001 Approvable letter.
- The 4-mg dose is deleted due to discontinuation.

***Comment:***
*Acceptable.*

### CLINICAL PHARMACOLOGY

- Revised per FDA's 4 February 2001 Approvable letter.
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets, including retaining the following text: "Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli."

***Comment:***
*Acceptable.*

### INDICATIONS AND USAGE

- Revised per FDA's 4 February 2001 Approvable letter from a list to a paragraph format, including editorial changes.
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets.

***Comment:***
*Acceptable.*

### CONTRAINDICATIONS

- Revised per FDA's 4 February 2001 Approvable letter.
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets, including retaining the contraindication "Systemic fungal infections" as well as adding the cross-reference "(see WARNINGS, *Fungal infections*)".

***Comment:***
*Acceptable.*

**WARNINGS**

- Revised per FDA's 4 February 2001 Approvable letter.
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets, including keeping the following additional text in the **WARNINGS, Endocrine** subsection: "Adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and 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. If the patient is receiving steroids already, dosage may have to be increased."

***Comment:***
*Acceptable.*

**PRECAUTIONS**

- Revised per FDA's 4 February 2001 Approvable letter, with one notable exception: The **Geriatric Use** statement requested by the FDA has been replaced with the version provided in the FDA Final Rule for Geriatric labeling 21 CFR 201.57(f)(10)(ii) because although both statements are consistent, the FDA Final Rule version includes a dosing caution. Also, an additional sentence was added based on supportive documentation Reference 2: Prevalence of Diabetes and Impaired Glucose Tolerance in Adult Hypopituitarism on Low Dose Oral Hydrocortisone Replacement Therapy, and Reference 3: Glucocorticoid-Induced Hypertension in the Elderly: Relation to Serum Calcium and Family History of Essential Hypertension. The **PRECAUTIONS, Geriatric Use** subsection reads as follows (strikethrough of old text and additional sentence underlined): "~~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.~~ Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.[2,3]"
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets, including:
  - Revisions to the **PRECAUTIONS, *Information for patients*** subsection to read (new text underlined): "Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision. As prolonged use may cause adrenal insufficiency and make patients dependent on corticosteroids, they should advise any medical attendants that they are taking corticosteroids and they should seek medical advice at once should they develop an acute illness including fever or other signs of infection. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including myalgia, arthralgia, and malaise."
  - The addition of the following sentence to the **PRECAUTIONS, Nursing Mothers** subsection: "Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

***Comment:***
*Acceptable.*

**PRECAUTIONS (continued)**

- Editorial changes in which titles were added to existing text of the current Decadron® Tablets labeling (package insert # 7921150) and the text inserted into the alphabetized list in the **PRECAUTIONS, Drug Interactions** subsection. These new text sections include:
  - *"Ephedrine:* Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage."
  - *"Phenytoin:* In post-marketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone co-administration, leading to alterations in seizure control."
  - *"Thalidomide:* Co-administration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use."

***Comment:***
*Acceptable.*

***Note from E. Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, Division of Pharmaceutical Evaluation III (DPE III):***
*"The Agency is highlighting individual drug data so that it is easy to locate within a label. The arrangement provided here is within the norm and represents a re-arrangement of information that is currently in the package insert. That is, no new information is being added to this sub-section of the label."*

- Editorial changes to the **PRECAUTIONS, Drug Interactions,** *Hepatic Enzyme Inducers* subsection for relative consistency with the current Decadron® Tablets labeling (package insert # 7921150) to read (new text underlined): "*Hepatic Enzyme Inducers, Inhibitors and Substrates:* Drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity *(e.g., barbiturates, phenytoin, carbamazepine, rifampin)* may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 *(e.g., ketoconazole, macrolide antibiotics such as erythromycin)* have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP 3A4. Co-adminstration with other drugs that are metabolized by CYP 3A4 *(e.g., indinavir, erythromcyin)* may increase their clearance, resulting in decreased plasma concentration."
- Added the cross-reference, "(see Drug Interactions, *Hepatic Enzyme Inducers, Inhibitors and Substrates),*" to the **PRECAUTIONS, Drug Interactions,** *Antibiotics* subsection since macrolide antibiotics are also inhibitors and substrates of Cytochrome P450 3A4.
- Editorial change to the **PRECAUTIONS, Drug Interactions,** *Ketoconazole* subsection based on supportive documentation Reference 1 (See Summary IIa.): The Effects of Ketoconazole on Patients Receiving Concomitant Corticosteroids. The following sentence was added although it was rejected in the 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets: "In addition, ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal."

***Comment:***
*Acceptable.*
***Note:*** *"Co-administration" is misspelled in the* ***PRECAUTIONS, Drug Interactions,*** Hepatic Enzyme Inducers *subsection.*

***Note from E. Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, Division of Pharmaceutical Evaluation III (DPE III):***
*"The first part of this revision deals with the addition of new information regarding CYP P-450 induction and metabolism. The information contained in this section represents current thought and general information that is available from the open literature. In addition, part of the revision represents a re-arrangement of information that is currently in the package insert."*

**ADVERSE REACTIONS**
- Revised per FDA's 4 February 2001 Approvable letter.
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets, including the addition of the following sentence at the beginning of the section: "The following adverse reactions have been reported with DECADRON or other corticosteroids."

***Comment:***
*Acceptable.*

**OVERDOSAGE**
Revised per FDA's 4 February 2001 Approvable letter, but changed to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets so that the section reads (strikethrough of 4 February 2001 Approvable letter text): "Treatment of ~~acute~~ overdosage is ~~by immediate gastric lavage or emesis followed~~ by-supportive and symptomatic therapy. In the case of acute overdosage, according to the patient's condition, supportive therapy may include gastric lavage or emesis. ~~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.~~"

***Comment:***
*Acceptable.*

**DOSAGE AND ADMINISTRATION**
- Revised per FDA's 4 February 2001 Approvable letter, with the exception of a minor editorial revision and that for the purpose of maintaining consistent nomenclature throughout the labeling, "glucocorticoids" has been changed to corticosteroids" in the following sentence: *"For the purpose of comparison, the following is the equivalent milligram dosage of the various ~~glucocorticoids~~ corticosteroids."*
- Revised to be consistent with FDA's 26 November 2002 Approvable letter for NDA 8-506 Hydrocortone® Tablets.
- Regarding the dosing schedule for combining parenteral and oral therapy, the trade name DECADRON Phosphate Injection is deleted and the established name of Dexamethasone Sodium Phosphate injection, USP 4 mg per mL is used alone since DECADRON Phosphate Injection is no longer marketed in the U.S.

***Comment:***
*Acceptable.*

**HOW SUPPLIED**

- Information regarding the 4-mg dose is deleted due to discontinuation.
- Revised per FDA's 4 February 2001 Approvable letter.

***Comment:***
*Acceptable.*

## Conclusion

Approval.

**Note:** "Co-administration" is misspelled in the **PRECAUTIONS, Drug Interactions,** *Hepatic Enzyme Inducers* subsection.

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## Review

Stacey N. Welch, M.A.
Regulatory Health Project Manager, DAAODP

## Comments

E. Dennis Bashaw, Pharm.D.
Biopharmaceutics Team Leader, DPE III

## Supervisory Concurrence

Carmen L. DeBellas, R.Ph.
Chief, Project Management Staff, DAAODP

Sharon H. Hertz, M.D.
Deputy Director, DAAODP

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/s/
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Stacey Welch
5/10/04 12:02:54 PM
CSO

Dennis Bashaw
5/11/04 09:51:06 AM
BIOPHARMACEUTICS

Carmen DeBellas
5/11/04 10:03:59 AM
CSO

Sharon Hertz
5/11/04 05:01:11 PM
MEDICAL OFFICER
I concur with this review.

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-664\S-062

Merck & Co., Inc.
Attention: Kenneth A. Kramer
Manager, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Mr. Kramer:

We acknowledge receipt of your November 29, 2004, submission containing final printed labeling in response to our May 17, 2004, letter approving your supplemental new drug application for Decadron™ (dexamethasone) 0.5 mg and 0.75 mg tablets.

We have reviewed the labeling that you submitted in accordance with our May 17, 2004, letter and we find it acceptable.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2516.

Sincerely,

*{See appended electronic signature page}*

Sharon H. Hertz, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/
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Sharon Hertz
2/14/05 12:27:52 PM

**Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products**

# REGULATORY PROJECT MANAGER REVIEW

**Application Number:** NDA 11-664/S-062

**Name of Drug:** Decadron™ (dexamethasone) 0.5 mg and 0.75 mg tablets

**Applicant:** Merck & Co, Inc.

## Material Reviewed: Final printed label

**Submission Date(s):** November 29, 2004

**Receipt Date(s):** November 30, 2004

## Background and Summary

Merck submitted NDA Supplement 062 on August 26, 2003. The FDA sent an Approval Letter dated May 17, 2004 pending upon the spelling correction of "Co-adminstration" under PRECAUTIONS.

## Review

The Agency's suggested change from Approval Letter dated May 17, 2004 was completed. We note that the font of sub-headings was updated from **bold** to *italicized.* The final printed label also removed an inappropriate comma under Information for Patients. The final printed label is acceptable.

## Conclusions

An Acknowledge and Retain letter will be sent to sponsor.

Nancy Clark, PharmD
Regulatory Project Manager

Supervisory Comment/Concurrence:

_____

Carmen DeBellas, RPh
Chief, Project Management Staff

Drafted: NC 2.9.05
Revised/Initialed:
Finalized:
Filename: FA 11.29.04

**CSO LABELING REVIEW**

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/s/
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Nancy Clark
2/9/05 03:17:08 PM
CSO

Carmen DeBellas
2/10/05 09:20:28 AM
CSO

Kenneth A. Kramer
Manager
Regulatory Affairs-Domestic

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 484 344 3000
Fax 484 344 2516

November 29, 2004

MERCK
Research Laboratories

Brian E. Harvey, M.D., Ph.D. - Acting Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Harvey:

**NDA 11-664/S-062: DECADRON™ Tablets**
**(Dexamethasone)**

**FINAL PRINTED LABELING for Approved Supplemental NDA 11-664/S-062**

Reference is made to the Supplemental/New Drug Application cited above. Reference is also made to the Agency's Approval letter of May 17, 2004, requesting Final Printed Labeling identical to the labeling submitted on August 26, 2003.

As per the Agency's request in the May 17, 2004 Approval Letter, the Final Printed Labeling submitted herewith also incorporates the minor editorial revisions indicated in that letter. Please also note that although the labeling is identical in content to the version approved in the referenced FDA Approval Letter, the font of the sub-headings has been updated from **bolded** to *italicized* in accordance with the company's current standard label style/format guidelines.

As indicated on the attached Form FDA 356h, this submission provides Final Printed Labeling for the approved supplemental New Drug Application for DECADRON™ Tablets. The Statement of Organization following this letter describes the sections contained in this application.

With this submission is the following item:

Labeling
I. Final Printed Package Insert [#7921151]

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Nancy A. Clark, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Ken Kramer (484-344-3000) or, in my absence, Tamra L. Goodrow, Ph.D. (484-344-3051).

Sincerely yours,

Mary Beth Higley for

Kenneth A. Kramer
Manager, Regulatory Affairs

Enclosure: CD

Federal Express #1

Desk Copy: Nancy A. Clark, Regulatory Project Manager (Cover Letter)
HFD 550, Rm. N345
Federal Express #2