PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-DEXAMETHASONE

Dexamethasone Tablets

Tablet, 0.5 mg and 4 mg, oral

USP

Corticosteroid

APOTEX INC.

150 Signet Drive

Weston, Ontario

M9L 1T9

Date of Initial Authorization:
JAN 05, 2004

Date of Revision:
MAR 16, 2022

Submission Control Number: 258219

RECENT MAJOR LABEL CHANGES

1 Indications, 1.2 Geriatrics	03/2022
7 Warnings and Precautions, 7.1.4 Geriatrics	03/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-DEXAMETHASONE (dexamethasone) is indicated for:

- **Allergic states:** Control of severe or incapacitating allergic conditions not responsive to adequate trials of conventional treatment: seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, serum sickness, drug hypersensitivity reactions.
- **Rheumatic disorders and collagen diseases:** As adjunctive therapy for short-term administration (for acute episode or exacerbation) in: psoriatic and rheumatoid arthritis including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy), ankylosing spondylitis, acute and subacute bursitis, acute non-specific tenosynovitis, acute gouty arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, epicondylitis; for exacerbation or maintenance therapy in selected cases of systemic lupus erythematosus, acute rheumatic carditis, systemic dermatomyositis, polymyositis, polymyalgia rheumatica, giant cell arteritis.
- **Dermatologic diseases:** Pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, mycosis fungoids, severe psoriasis, severe seborrheic dermatitis.
- **Ophthalmic diseases:** Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, anterior segment inflammation, diffuse posterior uveitis and choroiditis, optic neuritis, sympathetic ophthalmia.
- **Endocrine disorders:** Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; nonsuppurative thyroiditis; hypercalcemia associated with cancer.
- **Respiratory diseases:** Symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means, berylliosis, fulminating or disseminated pulmonary tuberculosis when concurrently accompanied by appropriate antituberculous chemotherapy, aspiration pneumonitis, pulmonary emphysema where bronchospasm or bronchial edema plays a significant role, diffuse interstitial pulmonary fibrosis (Hamman-Rich syndrome).
- **Hematologic disorders:** Idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, erythroblastopenia (RBC anemia), congenital (erythroid) hypoplastic anemia.
- **Neoplastic diseases:** For palliative management of: leukemias and lymphomas in adults, acute leukemia of childhood.

- **Edematous states:** To induce a diuresis or remission of proteinuria in the nephrotic syndrome without uremia, of the idiopathic type or that due to lupus erythematosus.
- **Nervous system:** May be used to treat patients with cerebral edema associated with primary or metastatic brain tumors, neurosurgery, head injury, pseudotumor cerebri and cerebral vascular accident (acute stroke) excluding intracerebral hemorrhage. May also be used in the preoperative preparation of patients with increased intracranial pressure secondary to brain tumors or for palliation of patients with inoperable or recurrent brain neoplasms.
- **Gastrointestinal diseases:** As adjunctive therapy in the treatment of ulcerative colitis and regional enteritis.
- **Miscellaneous:** Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement; postoperative dental inflammatory reactions. During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus, acute rheumatic carditis. In combination with ondansetron for the management of nausea and vomiting associated with cisplatin and non-cisplatin emetogenic chemotherapy.

APO-DEXAMETHASONE is also used in the diagnostic testing of adrenocortical hyperfunction and antenatal prophylaxis of neonatal respiratory distress.

1.1 Pediatrics

Pediatrics (Infants and Children): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of APO-DEXAMETHASONE in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 4.1 Dosing Considerations, 7.1.3 Pediatrics, 8.1 Adverse reaction Overview.

1.2 Geriatrics

The therapeutic experience in this population is limited. Therefore, APO-DEXAMETHASONE should be used with caution in geriatric patients.

2 CONTRAINDICATIONS

APO-DEXAMETHASONE is contraindicated in:

- Patients who are hypersensitive to dexamethasone or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with systemic fungal infections. See 7 WARNINGS AND PRECAUTIONS.
- Administration of live virus vaccines in patients receiving immunosuppressive corticosteroid doses. See Infections:

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Corticosteroid therapy is an adjunct to, not a replacement of conventional therapy, which should be instituted as indicated.
- Dosage must be decreased or therapy discontinued gradually when administration has been continued for more than a few days.
- In acute conditions where prompt relief is urgent, large doses are permissible and may be mandatory for a short period. When symptoms have been suppressed adequately, dosage should be maintained at the minimum amount capable of providing sufficient relief without excessive hormonal effects.
- Chronic conditions are subject to periods of spontaneous remission. When such periods occur, corticosteroids should be discontinued gradually.
- Routine laboratory studies such as urinalysis, 2-hourpost-prandial blood sugar, determinations of blood pressure and body weight, and a chest x-ray should be carried out at regular intervals during prolonged therapy. Periodic determinations of serum potassium are advisable if large doses are being used.

4.2 Recommended Dose and Dosage Adjustment

Dosage requirements are variable and must be individualized according to the severity of the disease and the response of the patient. The usual initial dosage varies from 0.5 to 15 mg per day depending on the disease being treated. For infants and children, the recommended doses usually will have to be reduced, but dosage should be dictated by the severity of the condition rather than by age or body weight.

Patients may be transferred to dexamethasone from any other glucocorticoid with the proper adjustment in dosage. The following milligram equivalents facilitate changing to dexamethasone from other glucocorticoids.

Dexamethasone tablets milligram (mg) equivalents				
Dexamethasone	Methyl-prednisolone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

Milligram for milligram, dexamethasone is approximately equivalent to betamethasone, 4 to 6 times more potent than methylprednisolone and triamcinolone, 6 to 8 times more potent than prednisone and prednisolone, 25 to 30 times more potent than hydrocortisone, and about 35 times more potent than cortisone. At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

In chronic, usually nonfatal diseases including endocrine and chronic rheumatic disorders, edematous states, respiratory and gastrointestinal diseases, some dermatologic diseases and hematologic disorders, start with a low dose (0.5 to 1 mg a day) and gradually increase dosage to the smallest amount that gives the desired degree of symptomatic relief.

Dosage may be administered 2, 3 or 4 times a day.

In congenital adrenal hyperplasia, the usual daily dose is 0.5 to 1.5 mg.

In acute, nonfatal diseases, including allergic states, ophthalmic diseases, acute and subacute rheumatic disorders, dosage ranges between 2 and 3 mg a day, however, higher doses are necessary in some patients. Since the course of these conditions is self-limited, prolonged maintenance therapy is not usually necessary.

Antiemetic prophylaxis during emetogenic chemotherapy: dexamethasone administered concomitantly with ondansetron has been demonstrated to achieve enhanced efficacy for antiemetic prophylaxis during emetogenic chemotherapy. Various dosing schedules have been used in clinical studies; however, the following is suggested for this combination: 8 to 20 mg of dexamethasone infused over 5 to 15 minutes just prior to chemotherapy, followed by 4 mg of dexamethasone orally every 4 to 6 hours, or by 8 mg orally every 8 hours, and tapered in either strength or frequency of administration over 2 to 3 days. In general the total treatment duration for this indication should not exceed 5 days beyond chemotherapy. Alternatively, injectable dexamethasone can be infused intravenously in lieu of an oral formulation of dexamethasone using various schedules.

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders (e.g., acute allergic rhinitis, acute attacks of seasonal allergic bronchial asthma, urticaria medicamentosa, and contact dermatoses), the following dosage schedule, combining parenteral and oral therapy, is suggested.

Dosage schedule			
		Total daily dosage	Number of 0.5 mg tablets
1st day	1 or 2 mL, intramuscular dexamethasone phosphate injection (4 mg / mL)	4 or 8 mg	
2nd day	2 tablets dexamethasone (0.5 mg) twice a day	2 mg	4
3rd day	2 tablets dexamethasone (0.5 mg) twice a day	2 mg	4
4th day	1 tablet dexamethasone (0.5 mg) twice a day	1 mg	2
5th day	1 tablet dexamethasone (0.5 mg) twice a day	1 mg	2
6th day	1 tablet dexamethasone (0.5 mg) / day	0.5 mg	1
7th day	1 tablet dexamethasone (0.5 mg) / day	0.5 mg	1
8th day	Follow-up visit		

In chronic, potentially fatal diseases such as systemic lupus erythematosus, pemphigus, symptomatic sarcoidosis, the recommended initial dosage is 2 to 4.5 mg a day; higher doses may be necessary in some patients.

When the disease is acute and life-threatening (e.g., acute rheumatic carditis, crisis of systemic lupus erythematosus, severe allergic reactions, pemphigus, neoplastic diseases), the initial dosage is between 4 and 10 mg a day, administered in at least 4 divided doses.

Epinephrine is the drug of immediate choice in severe allergic reactions. Dexamethasone is useful either concurrently or as supplementary therapy.

In cerebral edema, when maintenance therapy is required. For palliative management of patients with recurrent or inoperable brain tumors, a dosage of 2 mg, 2 or 3 times a day may be effective. The smallest dosage necessary to control cerebral edema should be utilized.

In the adrenogenital syndrome, daily dosages of 0.5 to 1.5 mg may keep children in remission and prevent the recurrence of abnormal excretion of 17-ketosteroids.

As massive therapy in certain conditions, such as acute leukemia, the nephrotic syndrome, and pemphigus, the recommended dosage is from 10 to 15 mg a day. Patients receiving such a high dosage must be observed very closely for the appearance of severe reactions.

Dexamethasone Suppression Tests

Give 1 mg 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 dexamethasone orally every 6 hours for 48 hours. Twenty-four-hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

Test to distinguish Cushing's syndrome due to pituitary ACTH excess from Cushing's syndrome due to other causes. Give 2 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four-hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

4.4 Administration

No special considerations regarding administration.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

There is no known antidote but gastric lavage should be performed. Acute overdose even after ingestion of large doses is rarely a clinical problem. Continuous overdosage requires careful reduction of dosage in order to prevent the occurrence of acute adrenal insufficiency.

Anaphylactic and hypersensitivity reactions depending on their severity, may be treated with antihistamines with or without epinephrine. General supportive measures should also be employed.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 0.5 mg, 4 mg of dexamethasone	Anhydrous lactose, corn starch, and magnesium stearate APO-DEXAMETHASONE 0.5 mg tablets also contain the non-medicinal ingredient D & C Yellow #10 Aluminium Lake 14-18 %.

APO-DEXAMETHASONE 0.5 mg tablets: Each yellow, pentagonal, flat faced, bevelled-edge tablet, engraved "APO" over ".5" on one side, scored on the other side, contains 0.5 mg dexamethasone. Available in bottles of 100's.

APO-DEXAMETHASONE 4 mg tablets: Each white, pentagonal, flat, bevelled-edge tablet, engraved "APO" over "4" on one side, scored on the other side, contains 4 mg dexamethasone. Available in bottles of 50's and 100's.

7 WARNINGS AND PRECAUTIONS

General

Because complications of treatment with corticosteroids are dependent on the dosage regimen, a risk/benefit decision must be made in each individual case with respect to dose and duration of treatment and whether daily or intermittent therapy should be used. The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Cardiovascular

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 and Metabolism

Adrenal suppression:

Following prolonged therapy, abrupt discontinuation may result in withdrawal syndrome and secondary adrenocortical insufficiency. Symptoms of adrenal insufficiency resulting from rapid withdrawal include: nausea, fatigue, anorexia, dyspnea, hypotension, hypoglycemia, myalgia, fever, malaise, arthralgia, dizziness, desquamation of skin and fainting. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any stressful situation occurring during that period, reinstitute hormone therapy. If the patient is receiving corticosteroids already, the dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid may need to be used.

Drug-induced secondary 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, corticosteroid therapy should be reinstituted or the current dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. There is an enhanced effect of corticosteroids in patients with hypothyroidism.

Fluid and electrolyte balance:

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention and increased potassium excretion. 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.

Gastrointestinal

The association between peptic ulceration and corticosteroid therapy remains controversial. However, corticosteroid therapy may mask the symptoms of peptic ulcer. Perforation or hemorrhage may occur without significant pain.

Corticosteroids should be used with caution in patients with diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer and in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection.

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

Steroids should be used with caution in: nonspecific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer, renal insufficiency; hypertension; osteoporosis; and

myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

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

Immune

Immunosuppression:

Patients being treated with corticosteroids should not be vaccinated against smallpox. Other immunization procedures should generally not be undertaken in these patients, especially those on high doses, because of possible neurological complications and a lack of antibody response. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy. Corticosteroids may suppress reactions to skin tests.

Infections:

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

Administration of live virus vaccines is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

The use of dexamethasone 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.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. If corticosteroids have to be used in the presence of bacterial infections, institute appropriate anti-infective therapy. Patients exposed to certain infections (e.g., measles, chickenpox) should seek medical advice. 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 due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

Musculoskeletal

Avascular or aseptic necrosis of the femoral head has been associated with long-term

corticosteroid treatment; however, it has also occurred in patients receiving high dose, short-term therapy. This adverse effect is more likely to occur in patients with a predisposing illness such as rheumatoid arthritis or systemic lupus erythematosis.

Neurologic

In cerebral malaria, the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

When Dexamethasone is used in myasthenia gravis, hospitalization with careful observation is recommended because a transient worsening of symptoms possibly leading to respiratory distress may precede clinical improvement.

Ophthalmologic

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

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

Psychiatric

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations; these reactions are sometimes seen following sharp decreases in corticosteroid dosage or during pulse therapy. Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Renal

Renal function impairment: Edema may occur in the presence of renal disease with a fixed or decreased glomerular filtration rate. A degree of caution is advised when corticosteroids are used in patients with renal insufficiency, acute glomerulonephritis and chronic nephritis.

Reproductive Health: Female and Male Potential

- **Fertility**

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

- **Teratogenic Risk**

  See 7.1.1 Pregnant Women.

Sensitivity/Resistance

Hypersensitivity:

Rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Some corticosteroid products contain tartrazine and sodium bisulfite, both of which may cause severe allergic reactions in susceptible individuals.

APO-DEXAMETHASONE contains lactose and caution should be exercised in patients with a known or suspected hypersensitivity to cow's milk or its components or other dairy products.

7.1 Special Populations

7.1.1 Pregnant Women

Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of child-bearing potential requires that the benefits of the drug be carefully weighed against the potential risks to both mother and fetus. Corticosteroids cross the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

7.1.2 Breast-feeding

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

7.1.3 Pediatrics

Prolonged therapy with corticosteroids in infants and children should be avoided if possible since corticosteroids may suppress growth. If corticosteroid therapy is deemed essential, institute alternate day therapy should be considered to minimize this side effect. Growth and development should be closely monitored.

7.1.4 Geriatrics

The adverse effects of systemic corticosteroids can have serious consequences especially in old age, mainly osteoporosis, hypertension, hypokalemia, diabetes, susceptibility to infection and skin atrophy. Routine screening of geriatric patients, including regular assessments of bone mineral density along with regular review of the dose is recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Fluid and electrolyte disturbances: sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension. See 7 WARNINGS AND PRECAUTIONS.

Musculoskeletal: muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture. See 7 WARNINGS AND PRECAUTIONS.

Gastrointestinal: nausea, vomiting, anorexia which may result in weight loss; increased appetite which may result in weight gain; diarrhea or constipation, abdominal distention, pancreatitis, gastric irritation and ulcerative esophagitis; peptic ulcer with possible perforation and hemorrhage; perforation of the small and large bowel particularly in inflammatory bowel diseases. See 7 WARNINGS AND PRECAUTIONS.

Dermatologic: impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; striae; hirsutism; acneiform eruptions; suppressed reactions to skin tests; hypersensitivity reactions such as allergic dermatitis, urticaria, angioneurotic edema.

Neurologic: seizures; increased intracranial pressure with papilledema (pseudotumor cerebri) in association with withdrawal of corticosteroid therapy; convulsions; vertigo; headache; psychic disturbances; neuritis; paresthesias. See 7 WARNINGS AND PRECAUTIONS.

Endocrine: decreased carbohydrate tolerance; hyperglycemia; glycosuria; increased requirements for oral hypoglycemics or insulin in diabetes; manifestations of latent diabetes mellitus; menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; hirsutism; increased sweating. See 7 WARNINGS AND PRECAUTIONS.

Ophthalmic: increased intraocular pressure; glaucoma; exophthalmos; posterior subcapsular cataracts. See 7 WARNINGS AND PRECAUTIONS.

Metabolic: negative nitrogen balance due to protein catabolism.

Psychologic: hallucinations; psychosis; euphoria; mood changes.

Cardiovascular: thromboembolism; fat embolism; hypercholesterolemia; accelerated atherosclerosis; cardiac arrhythmias or ECG changes due to potassium deficiency; syncope; aggravation of hypertension; myocardial rupture following recent myocardial infarction; reports of cardiac arrhythmias, fatal arrest or circulatory collapse following rapid administration of intravenous methylprednisolone greater than 0.5 g given over a period of less than 10 minutes. See 7 WARNINGS AND PRECAUTIONS.

Hematologic: leukocytosis, thrombocytopenia, lymphopenia.

Others: hypersensitivity; thrombophlebitis; weight gain; increased appetite; nausea; malaise; hiccups; necrotizing angiitis; aggravation or masking of infections; insomnia; anaphylactoid reactions. See 2 CONTRAINDICATIONS.

8.5 Post-Market Adverse Reactions

Information is not available.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and may be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. Exposed patients should be advised to seek medical advice without delay. See 9.4 Drug-Drug Interactions.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 1 - Established or Potential Drug-Drug Interactions

Dexamethasone	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) and other NSAIDS (nonsteroidal anti-inflammatory agents)	T		ASA and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinemia.

Dexamethasone	Source of Evidence	Effect	Clinical comment
Phenytoin, phenobarbital, ephedrine and rifampin	T	↓ corticosteroids	Phenytoin, phenobarbital, ephedrine and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.
Indomethacin	T		False- negative results in the dexamethasone suppression test in patients being treated with indomethacin have been reported.
Coumarin anticoagulants	CT	Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.	The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants.
Potassium-depleting diuretics	T		When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

Dexamethasone	Source of Evidence	Effect	Clinical comment
Immunosuppressants	T	↑infections See 9.1 Serious Drug Interactions.	If exposed to measles, prophylaxis with i.m. pooled immunoglobulin (IG) may be indicated. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated (see the respective Product Monographs for VZIG and IG for complete prescribing information). If chickenpox develops, treatment with antiviral agents should be considered.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Corticosteroids may decrease I^{131} uptake and produce false negative results in the nitroblue tetrazolium test for systemic bacterial infection. These tests should be interpreted with caution during the administration of corticosteroids.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is therefore, particularly suitable for the use in patients with cardiac failure and hypertension.

Its anti-inflammatory potency is 7 times greater than prednisolone and, like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

Dexamethasone has a biological half-life of 36 - 54 hours and therefore is suitable in conditions where continuous glucocorticoid action is required.

10.2 Pharmacodynamics

Information is not available.

10.3 Pharmacokinetics

Absorption:

Dexamethasone is well absorbed when given by mouth; peak plasma levels are reached between 1 and 2 hours after ingestion and show wide interindividual variations. The mean plasma half-life is 3.6 ± 0.9 h.

Distribution:

Dexamethasone is bound (to about 77%) to plasma proteins, mainly albumins. Percentage protein binding of dexamethasone, unlike that of cortisol, remains practically unchanged with increasing steroid concentrations. Corticosteroids are rapidly distributed to all body tissues. They cross the placenta and may be excreted in small amounts in breast milk.

Metabolism:

Dexamethasone is metabolised mainly in the liver but also in the kidney.

Elimination:

Dexamethasone and its metabolites are excreted in the urine.

Special Populations and Conditions:

Information is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C to 30°C.

APO-DEXAMETHASONE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

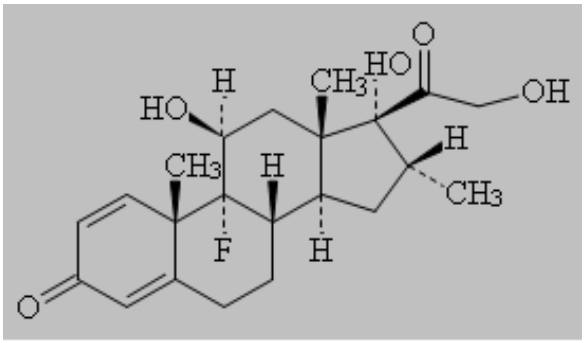
Proper name: Dexamethasone

Chemical name: 1) Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11β, 16α)-

2) 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Molecular formula and molecular mass: $C_{22}H_{29}FO_5$ and 392.5 g/mol

Structural formula:



Physicochemical properties: White to practically white, odorless, crystalline powder. Is stable in air. Melts at about 250°, with some decomposition. Practically insoluble in water; sparingly soluble in acetone, in alcohol, in dioxane, and in methanol; slightly soluble in chloroform; very slightly soluble in ether.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

A comparative bioavailability study was performed using healthy adult volunteers. The rate and extent of absorption of dexamethasone were measured and compared following administration of a 4 mg dose of either Apo-Dexamethasone 4 mg tablets or Decadron® 4 mg tablets under fasting conditions. The results from measured data are summarized as follows:

Dexamethasone (1 x 4 mg) From measured data Geometric Mean Arithmetic Mean (CV %)			
Parameter	Geometric Mean Arithmetic Mean (CV%)		% Ratio of Geometric Means**
	Apo-Dexamethasone	Decadron®†	
AUC_T (ng•hr/mL)	166 174 (32)	175 182 (31)	94.9
AUC_I (ng•hr/mL)	169 178 (32)	178 186 (33)	94.9
C_{max} (ng/mL)	27.2 27.9 (22)	29.7 30.4 (23)	91.4
T_{max} (hr)*	1.56 (41)	1.46 (38)	-
$t_{1/2}$ (hr)*	4.03 (17)	4.09 (15)	-

* Arithmetic means (CV%).
** Based on the least squares estimate.
† Decadron® is manufactured by Merck Frosst Canada & Co., and was purchased in Canada.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Information is not available.

Carcinogenicity: Information is not available.

Genotoxicity: Information is not available.

Reproductive and Developmental Toxicology: Information is not available.

Special Toxicology: Information is not available.

Juvenile Toxicity: Information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1 ratio-DEXAMETHASONE (dexamethasone USP), Tablet, 0.5 mg and 4 mg, Submission Control No: 162516, Product Monograph, Teva Canada Limited. Date of Revision: February 26, 2013.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-DEXAMETHASONE

Dexamethasone tablets USP

Read this carefully before you start taking **APO-DEXAMETHASONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-DEXAMETHASONE**.

What is APO-DEXAMETHASONE used for?

APO-DEXAMETHASONE is used:

- in the treatment of various conditions. These include allergy or inflammation;
- to replace corticosteroid hormone when the body does not produce enough. This is due to problems with the adrenal glands;
- for diagnostic testing of:
    - adrenocortical hyperfunction. This is a condition where the adrenal glands produce too much of certain hormones.
    - neonatal respiratory distress of fetus during pregnancy. This is a breathing disorder in newborns caused by immature lungs.

How does APO-DEXAMETHASONE work?

APO-DEXAMETHASONE contains dexamethasone as the active ingredient. Dexamethasone belongs to a group of medicines called corticosteroids. It decreases the body's immune response to some diseases. This reduces symptoms such as swelling and redness.

What are the ingredients in APO-DEXAMETHASONE?

Medicinal ingredients: dexamethasone

Non-medicinal ingredients: anhydrous lactose, corn starch, D&C Yellow #10 Aluminium Lake 14-18 % (in 0.5 mg tablet only) and magnesium stearate.

APO-DEXAMETHASONE comes in the following dosage forms:

Tablets: 0.5 mg and 4 mg.

Do not use APO-DEXAMETHASONE if:

- you are allergic to dexamethasone or any of the other ingredients of this medicine.
- you have fungal infection that affects the whole body.
- you are planning to receive a type of vaccine called live vaccines.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-DEXAMETHASONE. Talk about any health conditions or problems you may have, including if you:

- have or have had any type of infection, like:
    - parasitic infection (ex. cerebral malaria, or amebiasis)
    - bacterial infection (ex. tuberculosis)
    - viral infection (ex. eye herpes)
    - fungal infection that affects the whole body.
- have high blood pressure.
- have heart disease or recently had a heart attack.
- have low levels of potassium and calcium in your blood.
- have an underactive thyroid gland.
- have a bowel disorder or a stomach (peptic) ulcer.
- have osteoporosis (thinning of the bones).
- have myasthenia gravis (a condition causing weak muscles).
- have liver problems (liver cirrhosis).
- have received vaccines for smallpox, measles or chickenpox in the past.
- have eye problems like cataract (clouding of the lens in the eye leading to a decrease in vision) or glaucoma (raised eye pressure).
- have had certain mental or mood conditions like feeling high, sleeping problems, mood swings or severe depression.
- have kidney problems.
- have low sperm count and decreased motility of sperm cells.
- have lactose intolerance.
- have conditions like rheumatoid arthritis or systemic lupus erythematosus.
- are 65 years of age or older.

Other warnings you should know about:

Stopping treatment:

- If you suddenly stop taking APO-DEXAMETHASONE, you may experience:
    - Adrenal insufficiency, a condition where your body does not make enough of the cortisol hormone.
    - "Withdrawal syndrome". This includes symptoms such as nausea, fatigue, decreased appetite, shortness of breath, low blood pressure, low blood sugar levels, muscle pain, fever, general discomfort, joint pain, dizziness, peeling of skin and fainting.

- Tell your healthcare professional right away if you experience any symptoms of withdrawal after changing or stopping your treatment. Some of these symptoms can last for months after you stop taking APO-DEXAMETHASONE.

Infections:

- Treatment with APO-DEXAMETHASONE may reduce your body's ability to fight infections. This can sometimes lead to infections caused by germs that rarely cause infection under normal situations.
- Taking APO-DEXAMETHASONE with other medicines that weakens your immune system may increase your risk of infections.
- During treatment, avoid contact with anyone who has chickenpox, shingles or measles. If you were in contact with any of these infections, contact your healthcare professional right away, even if there are no symptoms.

Female patients:

- If you are pregnant or planning on becoming pregnant while taking APO-DEXAMETHASONE, there are specific risks that you should discuss with your healthcare professional.
- This medicine can cross the placenta and harm your baby.
- Tell your healthcare professional right away if you become pregnant while taking APO-DEXAMETHASONE.
- APO-DEXAMETHASONE can pass into your breast milk and harm your baby. Before taking this medicine, talk to your healthcare professional about the best way to feed your baby during treatment.

Children (less than 18 years of age): APO-DEXAMETHASONE can affect growth in children. Your healthcare professional will regularly monitor growth and development in growing children.

Suppressed reaction to lab tests: If you are doing the following lab tests, tell your healthcare professional that you are taking APO-DEXAMETHASONE. It may interfere with the results.

- Skin test for allergy
- Test for bacterial infection

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with APO-DEXAMETHASONE. They may:

- Check your blood pressure and body weight.
- Take a chest x-ray at regular intervals, during long-term treatment.
- Do urine tests and blood tests to check your blood sugar (2 hours after you start eating a meal), potassium levels and blood health.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-DEXAMETHASONE:

- acetylsalicylic acid, indomethacin or other Non-Steroidal Anti-Inflammatory Drugs used to reduce fever, pain and inflammation.
- phenytoin used to treat epilepsy.
- phenobarbital used to to aid sleep and relieve anxiety.
- ephedrine used as nasal decongestant.
- rifampin, an antibiotic used to treat tuberculosis.
- coumarin anticoagulants used to prevent the formation of blood clots.
- potassium-depleting diuretics used to treat high blood pressure.
- immunosuppressants used to treat auto immune disorders.
- vaccination with live vaccines.
- other corticosteroids.

How to take APO-DEXAMETHASONE:

- Take APO-DEXAMETHASONE exactly as your healthcare professional tells you.
- Take by mouth.

Usual dose:

APO-DEXAMETHASONE used as treatment:

- Your healthcare professional will decide the best dosage for you based on your condition. They will give you the lowest dose possible for your treatment.
- When your condition has improved, your healthcare professional will reduce your dose gradually. Do NOT change your dose or stop taking APO-DEXAMETHASONE before talking to your healthcare professional.
- Your healthcare professional will monitor your health. They may change your dose, temporarily or completely stop treatment. This may happen if you:
    - Experience serious side effects; or
    - Your disease gets worse.

APO-DEXAMETHASONE used as diagnostic testing (dexamethasone suppression test):

- Your healthcare professional will decide the best dosage for you based on the condition they want to diagnose.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-DEXAMETHASONE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take a dose of APO-DEXAMETHASONE, take it as soon as you remember.
- If it is nearly time for the next dose, skip the missed dose. Take the next dose at the usual time.
- Do NOT take a double dose to make up for a forgotten dose.

What are possible side effects from using APO-DEXAMETHASONE?

These are not all the possible side effects you may have when taking APO-DEXAMETHASONE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- **Stomach and intestinal problems:**
  - nausea, vomiting
  - diarrhea, constipation
  - stomach irritation
  - abdominal pain
  - changes in appetite
- **Musculoskeletal problems:**
  - loss of muscle mass
  - muscle pain
  - malaise (feeling of general discomfort or uneasiness)
- **Nervous system problems:**
  - headache
  - dizziness
  - amnesia
  - vertigo
  - impaired sensation, strength, and reflexes
  - sensation of tingling, tickling, prickling, or burning of a person's skin
- **Psychiatric problems:**
  - drug dependence
  - abnormal behavior
  - irritability
  - difficulty sleeping
- **Skin problems including:**
  - thin fragile skin
  - rash
  - red spots containing blood
  - stretch marks
  - petechiae (reddish spot containing blood that appears in skin)
  - ecchymoses (discoloration of skin due to bleeding under the skin)
  - facial redness
  - abscess
- **Hormone and metabolism problems:**
  - suppression of growth in children
  - weight gain
  - abnormal fat deposits
  - acne
  - thinning hair
  - acne
  - increased sweating

- lightening or darkening of an area of skin
- hirsutism (a condition in women that results in excessive growth of dark or coarse hair in a male-like pattern),
- Slow wound healing
- hypopituitarism (a condition in which your pituitary gland fails to produce one or more of its hormones or does not produce enough of them).
- thyroid gland problems

- **Other**
  - high cholesterol
  - fatigue
  - hiccups

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
FREQUENCY UNKNOWN			
Edema: fluid retention, swelling of the hands, legs or feet, muscle pain or cramps		√	
Congestive Heart Failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, cough, rapid or irregular heartbeat			√
High blood pressure: Headache, shortness of breath, feeling unwell			√
Cushing's Syndrome (excess cortisol): round "moon face", rapid weight gain especially around the body, excess sweating, thinning of the skin, easy bruising, dry skin, stretch marks, muscle weakness, fat deposits between the shoulder blades (buffalo hump), wounds that are slow to heal		√	
Muscle weakness			√
Seizures: Convulsions or fits, with or without loss of consciousness			√
Osteoporosis (thin, fragile bones): broken bones,			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
bone/join pain, back pain that gets worse when standing or walking			
Hormonal changes: irregular menstrual periods	√		
Allergic reaction: fever, skin rash, hives, itching, difficulty in swallowing and breathing, swelling of the face, lips, tongue or throat			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
Stomach ulcer: heartburn, long lasting stomach pain, blood in stools and/or vomiting blood, loss of appetite and weight loss			√
Gastrointestinal perforation (a hole in the wall of your stomach or bowels): severe abdominal pain and tenderness, nausea, vomiting, chills or fever			√
Mental health problems: feeling depressed including thinking about suicide, feeling anxious, insomnia, confusion, hallucinations (seeing or hearing things that are not really there), euphoria (intense feelings of well-being, elation, happiness, excitement and joy), mood swings, personality changes, memory problems		√	
Diabetes (high blood sugar): increased thirst, frequent urination and hunger		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			√
Reactivation of tuberculosis: coughing blood, pain in the chest, loss of appetite, unexplained weight loss, fever, chills, night sweats			√
Eye problems: • **Glaucoma** (Increased intraocular pressure): increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, and changes in vision, Hazy or blurred vision, sudden sight loss. • **Cataracts**: clouding of the lens in the eye, blurry vision, dim vision and/or eye pain • **Central serous chorioretinopathy (CSCR):** blurry vision or other changes in vision		√	
Infections: fever, chills, feeling unwell, sore throat, body aches, fatigue			√
Abnormal blood cell counts: Increased count of white blood cells, low platelet count, low lymphocytes count	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about APO-DEXAMETHASONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html. Find the Product Monograph on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by APOTEX INC.

Last Revised MAR 16, 2022