PRESCRIBING INFORMATION

PrTEVA-PREDNISONE

Prednisone Tablets

5 mg and 50 mg

USP

Corticosteroid

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Date of Revision:
JAN 15 2025

Submission Control No: 288936

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THERAPEUTIC CLASSIFICATION

Corticosteroid

ACTION AND CLINICAL PHARMACOLOGY

Prednisone is a corticosteroid, which like other steroids, act by controlling the rate of synthesis of proteins. The corticosteroids react with receptor proteins in the cytoplasm of sensitive cells to form a steroid-receptor complex. The steroid receptor complex moves into the nucleus where it binds to chromatin. Information carried by the steroid or more likely by the receptor protein directs the genetic apparatus to transcribe RNA. Steroid hormones thus stimulate transcription and ultimately the synthesis of specific proteins.

The major physiologic actions of prednisone are: to increase liver glycogen deposition and to decrease the inflammatory response. Prednisone has some effects on sodium and fluid retention.

The mechanism of action is not fully established. It is theorized that the drug's anti-inflammatory effect is due to multiple mechanisms, including the inhibition of leukocyte migration to sites of tissue injury, the impairment of phagocytosis plus reduced capillary permeability. The drugs immunosuppressant effect is attributed to several factors, among them a transient lymphopenia especially of T-lymphocytes, and inhibition of immunoglobulin production of monocytes.

Prednisone is rapidly and completely absorbed from the intestinal tract. After oral administration, maximum plasma concentrations are reached in 1 to 2 hours. Once absorbed, the drug is approximately 75% bound to plasma proteins. The major route of

elimination is via the liver (t1/2=4 hr.); and the active drug disappears completely in about 12 hours.

In pharmacologic doses, systemically administered glucocorticoids suppress release of corticotropin (adrenocorticotropic hormone, ACTH) from the pituitary; thus the adrenal cortex ceases secretion of endogenous corticosteroids (secondary adrenocortical insufficiency). The degree and duration of hypothalamic-pituitary-adrenal (HPA) axis suppression produced by the drugs is highly variable among patients and depends on the dose, frequency and time of administration, and duration of glucocorticoid therapy. If suppressive doses of glucocorticoids are administered for prolonged periods, the adrenal cortex atrophies and patients develop cushingoid (hypercorticism) features and respond to stress like patients with primary adrenocortical insufficiency.

INDICATIONS AND CLINICAL USES

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.

Nonendocrine disorders: Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy), ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, epicondylitis.

Collagen diseases: During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus, acute rheumatic carditis, systemic dermatomyositis (polymyositis), polymyalgia rheumatica, giant cell arthritis.

Dermatologic diseases: pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, mycosis

fungoides, severe psoriasis.

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

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.

Respiratory diseases: Symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently **with** appropriate antituberculous chemotherapy, aspiration pneumonitis.

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.

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

CNS: Acute exacerbations of multiple sclerosis. Organ transplantation.
Miscellaneous: Tuberculous meningitis with subarachnoid block or impending

block when used concurrently with appropriate antituberculous chemotherapy, trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to prednisone.

WARNINGS

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

As sodium retention with resultant oedema and potassium loss may occur in patients receiving glucocorticoids, these agents should be used with caution, and only if strictly necessary, in patients with congestive heart failure. Glucocorticoids should also be used with caution in patients with hypertension, or renal insufficiency (See PRECAUTIONS).

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, glucocorticoids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed.

Fungal Infections: Glucocorticoids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see CONTRAINDICATIONS).

Thrombosis including venous thromboembolism has been reported to occur with glucocorticoids. As a result glucocorticoids should be used with caution in patients

who have or may be predisposed to thromboembolic disorders.

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

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.

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. Allergic reactions (e.g. angioedema) may occur.

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

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

The use of prednisone 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.

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain.

Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Growth may be suppressed in children receiving long-term daily, divided dose glucocorticoid therapy and use of such regimen should be restricted to the most urgent indications. Alternate day glucocorticoid therapy usually avoids or minimizes this side effect.

Host defenses are impaired in patients receiving large doses of glucocorticoids and this effect increases susceptibility to fungus infections as well as bacterial and viral infections.

Pregnancy and Lactation: Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. Adequate human reproduction studies have not been done with corticosteroids. Therefore, the use of this drug in pregnancy, nursing mothers or women of childbearing potential requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or fetus. Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy only if clearly needed.

Corticosteroids readily cross the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. There are no known effects of corticosteroids on labor and delivery. Corticosteroids are excreted in breast milk.

PRECAUTIONS

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.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

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

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

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.

ASA and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinemia.

Corticosteroids 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; or myasthenia gravis.

Because complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in

each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Drug Interactions: The pharmacokinetic interactions listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the dose of clearance of chronic high dose ASA. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when the corticosteroid is withdrawn. ASA should be used cautiously in conjunction with corticosteroids in patients suffering from hypothrombinemia. The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as, diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur.
The possibility of this interaction occurring with prednisone should be considered.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There is no evidence that corticosteroids are carcinogenic, mutagenic, or impair fertility.

Lactation: Some prednisone is excreted in breast milk.

Renal: As sodium retention with resultant oedema and potassium loss may occur in patients receiving glucocorticoids, these agents should be used with caution in patients with hypertension or renal insufficiency. Glucocorticoids should also be used with caution, and only if strictly necessary, in patients with congestive heart failure (See WARNINGS, Cardiovascular).

ADVERSE REACTIONS

Note: The following are typical for all systemic corticosteroids. Their inclusion in this list does not necessarily indicate that the specific event has been observed with this particular formulation.

Cardiac disorders: Cardiac failure congestive (in susceptible patients); Bradycardia; Cardiac arrest; Arrhythmia; Cardiomegaly; Circulatory collapse; Fat embolism; Hypertrophic cardiomyopathy in premature infants; Myocardial rupture following recent myocardial infarction Pulmonary oedema; Syncope; Tachycardia; Embolism; Thrombophlebitis; Vasculitis.

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

Musculoskeletal: steroid myopathy; muscle weakness; osteoporosis; pathologic fractures; vertebral compression fractures, aseptic necrosis.

Gastrointestinal: peptic ulcer with possible perforation and hemorrhage; gastric hemorrhage; pancreatitis; esophagitis; perforation of the bowel.

Dermatologic: impaired wound healing; petechiae and ecchymoses; thin fragile skin.

Metabolic: negative nitrogen balance due to protein catabolism.

Neurological: increased intracranial pressure; pseudotumor cerebri; psychic derangements and seizures.

Endocrine: menstrual irregularities; development of Cushingoid state; suppression of pituitary-adrenal axis; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes; suppression of growth in children.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure; exophthalmos. Immune System: masking of infections; latent infections becoming active; opportunistic infections; hypersensitivity reactions including anaphylaxis; may suppress reactions to skin tests.

Other: A steroid withdrawal syndrome seemingly unrelated to adrenocortical insufficiency and consisting of anorexia, nausea and vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss and/or hypotension has been reported following abrupt withdrawal of glucocorticoids. Symptoms often occurred while plasma glucocorticoid concentrations were still high but were falling rapidly; apparently the abrupt change in glucocorticoid concentration rather than a low concentration per se was responsible for the phenomenon. (See DOSAGE AND ADMINISTRATION).

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.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.

DOSAGE AND ADMINISTRATION

The initial dosage may vary from 5 to 60 mg of prednisone per day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, prednisone should be discontinued.

It should be emphasized that dosage requirements are variable and must be

individualized on the basis of the disease under treatment and the response of the patient.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the 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 prednisone for a period of time consistent with the patient's condition.

ADT-Alternate Day Therapy: Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticosteroid is administered every other morning. The purpose of this mode of therapy is to provide a patient requiring long-term, pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

Discontinuance of Therapy

Although high-dose glucocorticoid therapy used for only brief periods in emergency situations may be reduced and discontinued quite rapidly, withdrawal following long-term therapy with pharmacologic dosages of systemic glucocorticoids should be very gradual until recovery of HPA- axis function occurs. (See ACTION and CLINICAL PHARMACOLOGY).

Many methods of slow withdrawal or "tapering" have been described. In one suggested regimen, glucocorticoid dosage is decreased by the equivalent of 2.5-5 mg of prednisone every 3-7 days until the physiologic dose (e.g., 5 mg of

prednisone) is reached. Other recommendations state that decrements usually should not exceed 2.5 mg of prednisone (or its equivalent) every 1-2 weeks except in patients on alternate-day therapy in whom it may be possible to decrease dosage in decrements of 5 mg of prednisone at 1-to 2-week intervals. If the disease flares up during withdrawal, dosage may need to be increased and followed by a more gradual withdrawal. In addition, increased dosage will be required during periods of stress. When a physiologic dosage has been reached, it has been suggested that single 20 mg oral morning dose of hydrocortisone be substituted for whatever glucocorticoid the patient has been receiving. After 2-4 weeks, the dosage of hydrocortisone may be decreased by 2.5 mg every week until a single morning dosage of 10 mg daily is reached.

The time required for complete HPA function recovery following discontinuance of glucocorticoid therapy is variable. Tests of adrenal function may be used to measure recovery of adrenocortical function. Normal morning plasma cortisol concentrations (greater than 10 11gidL) indicate that basal pituitary adrenal function is adequate and that maintenance therapy can be discontinued. However, this does not assure that adrenal function has recovered sufficiently to adequately increase cortisol production in response to stress and therefore, supplemental glucocorticoids may still be required during stress. Complete recovery of HPA function generally can be assumed and supplementary therapy during stress can usually be discontinued when response to a corticotropin or cosyntropin test is normal.

OVERDOSAGE

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

AVAILABILITY OF DOSAGE FORMS

TEVA-PREDNISONE 5 mg tablets is available as a white scored tablet embossed with N and 5 on the same side. Supplied in bottles of 1000.

TEVA-PREDNISONE 50 mg tablets is available as a white scored tablet embossed with novo and 50 on the same side. Supplied in bottles of 100.

STABILITY AND STORAGE RECOMMENDATION

Store between 15°- 30°C.

MORE INFORMATION

If you want more information about TEVA-PREDNISONE:

- Talk to your healthcare professional
- Find the full Prescribing Information that is prepared for healthcare professionals by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by:
Teva Canada Limited
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Toronto, Ontario
Canada M1B 2K9
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Last Revised: JAN 15 2025