

APO-PREDNISONONE

Prednisone 1mg, 2.5mg, 5mg and 20mg Tablets

Presentation

APO-PREDNISONONE 1mg tablets are round, white, biconvex, 5.5mm in diameter and identified P over 1 on one side. Each tablet contains 1mg prednisone and typically weighs 80mg.

APO-PREDNISONONE 2.5mg tablets are round, white, biconvex, 6.0mm in diameter and identified P over 2.5 on one side. Each tablet contains 2.5mg prednisone and typically weighs 87mg.

APO-PREDNISONONE 5mg tablets are round, white, flat-faced with bevelled edges, 6.5mm in diameter and identified P over 5 on one side. Each tablet contains 5mg prednisone and typically weighs 94mg.

APO-PREDNISONONE 20mg tablets are round, pink, biconvex, 6.5mm in diameter and identified P over 20 with a breakline on one side. Each tablet contains 20mg prednisone and typically weighs 97mg.

Uses

Actions

Prednisone is a biologically inert glucocorticosteroid which is rapidly converted in the liver to its active metabolite prednisolone. Glucocorticosteroids chief pharmacological effects are upon gluconeogenesis, glycogen deposition and protein and calcium metabolism. Glucocorticoids possess marked anti-inflammatory, anti-allergic and anti-rheumatic properties where they decrease the vascular and cellular component of the inflammatory response. Immunosuppressant properties are also exhibited especially with pharmacological doses.

Prednisone is a potent therapeutic agent influencing the biochemical behaviour of most tissues in the body. When prednisone is compared with the naturally occurring glucocorticoids, cortisone and cortisol (hydrocortisone), its anti-inflammatory effects are 5 times more potent whilst its mineralocorticoid properties are less pronounced. The onset of action of prednisone varies considerably depending on the dose and condition for which it is used. Its duration of action is approximately 18 to 36 hours.

Pharmacokinetics

Prednisone is readily absorbed from the gastro-intestinal tract and has a preconversion biological half-life of about 60 minutes before hydroxylation in the liver to its active metabolite prednisolone. Prednisolone has a plasma half-life of 2 to 3 hours and is extensively bound to plasma proteins. There are wide inter-individual differences in the rate of metabolism of prednisolone. Prednisolone is metabolised primarily in the liver to biologically inactive metabolites (primarily the gluconide and sulphate). Prednisone is excreted in the urine as free and conjugated metabolites together with an appreciable amount of unchanged prednisolone. The conversion of prednisone is probably not diminished by liver disease.

Indications

Glucocorticoids are used to suppress the clinical manifestations of disease in a wide range of disorders such as: bronchial asthma, emphysema, pulmonary fibrosis, allergic skin reactions, blood disorders including auto-immune haemolytic anaemia and idiopathic thrombocytopenic purpura, selected collagen and rheumatic disorders (but rarely rheumatoid arthritis), connective tissue disorders such as arteritis and systemic lupus erythematosus, inflammatory bowel disease such as ulcerative colitis and Crohn's disease, some hepatic disorders such as chronic active hepatitis, nephritic syndrome and other renal disorders, selected inflammatory ocular diseases, acute exacerbations of eczema, exfoliate dermatitis and pemphigus, and some neurological disorders such as infantile seizures (epilepsy) and sub-acute demyelinating polyneuropathy.

Miscellaneous uses include raised intracranial pressure, sarcoidosis, the neonatal respiratory distress syndrome, the gastric acid aspiration syndrome, acute rheumatic fever with carditis and occasionally hypercalcaemia. Glucocorticoids may be used in conjunction with antineoplastic agents in regimens for the management of

malignant disease such as leukaemia. They are also used to suppress the rejection phenomenon in tissue transplants.

Dosage and Administration

The smallest dose which is effective or produces adequate control should be used since inhibition of corticotrophin secretion is related to dose and the duration of glucocorticoid therapy. Alternate day early-morning dosage regimens produce less suppression of the HPA (Hypothalamic-pituitary-adrenal) axis but may not always provide adequate control - this regimen is not recommended for treatment of haematological disorders, malignancies, ulcerative colitis or severe conditions.

It may be necessary to increase dosage temporarily during maintenance therapy or during a steroid withdrawal programme for flare-ups of the underlying disease or for major stress such as infection or trauma. When pharmacological doses of glucocorticoids are to be reduced or withdrawn the dosage must be tapered gradually; this will be limited by the underlying disease process and the recovery of the HPA axis. Sudden cessation can be dangerous.

Take with food and a full glass of water.

Adults:

The initial dose of prednisone is 10mg - 100mg daily in divided doses, as a single daily dose at 8.00am or as a double dose on alternate days.

The maintenance dose is usually 5mg to 20mg daily. The dose should be individualised according to the severity of the disease and the patient's response rather than by age or body weight. The usual adult prescribing limit is up to 250mg daily.

Short Term Therapy:

20mg to 40mg daily with dosage reductions of 2.5mg or 5mg every 2 to 4 days depending on response.

Children:

For infants and children the dosage should be governed by the severity and expected duration of the disease and reaction to medication rather than a strict adherence to the ratio indicated by age or bodyweight. For the treatment of adrenocortical insufficiency the USPDI recommends that doses be based on body surface area. Typically, for children over 18 months of age, initial dosage is 0.5mg/kg daily. This dosage can be doubled or trebled until definitive remission occurs. Maintenance dose is 0.125 - 0.25mg/kg daily.

Contraindications

Hypersensitivity to any ingredient
Systemic infections unless specific anti-infective therapy is given.
Live virus immunisation
Pancreatitis (except pancreatitis caused by sarcoidosis)

Warnings and Precautions

Ideally corticosteroid therapy should not be instituted until a definite diagnosis has been made since the clinical signs and symptoms of disease can be masked or inhibited.

Abrupt withdrawal of prednisone after chronic use may precipitate acute adrenal insufficiency as a result of the suppression of corticotrophin at the anterior pituitary. Symptoms of adrenal insufficiency include malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

The withdrawal symptoms may simulate a clinical relapse of the disease for which the patient is undergoing treatment. Withdrawal of prednisone should always be gradual, the rate depending on the individual patient's response, the dose and duration of therapy.

A degree of inhibition of hypothalmo-pituitary-adrenocortical function may persist for 6 to 12 months after prolonged high-dose treatment is withdrawn; steroid therapy may need to be re-instituted during periods of stress.

General Precautions

Caution is necessary when oral corticosteroids are used in patients with the following conditions and frequent monitoring is necessary:

- Hypertension
- Hypothyroidism
- Congestive Heart failure or recent myocardial infarction
- Liver failure
- Renal insufficiency
- Diabetes mellitus or in those with a family history of diabetes
- Osteoporosis
- Glaucoma
- Patients with a history of severe affective disorders particularly of steroid induced psychoses
- Epilepsy and/or seizure disorder
- Peptic ulceration
- Previous steroid myopathy
- Tuberculosis
- Patients with myasthenia gravis receiving anticholinesterase therapy since prednisone may decrease plasma anticholinesterase activity
- Patients with thromboembolic disorders
- Patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous physical activity
- Patients with Cushing's disease

Adrenocortical Insufficiency

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration and duration of therapy.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

During prolonged courses of corticosteroid therapy sodium intake may need to be reduced and calcium and potassium supplements may be necessary. Monitoring of fluid intake and output and daily weight records may give an early warning of fluid retention.

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly, therefore withdrawal of prednisone should always be gradual. A degree of adrenal insufficiency may persist for 6 to 12 months; therefore in any situation of stress occurring during that period steroid therapy may need to be reinstated. Since mineralocorticoid secretion may be impaired treatment with salt and/or a mineralocorticoid may also be needed.

During prolonged therapy, any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage.

Anti-inflammatory/ Immunosuppressive effects and Infection

Suppression of the inflammatory response and immune function increases susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognized when corticosteroids including prednisone are used. The immunosuppressive effects of glucocorticoids may result in activation of latent infection or exacerbation of intercurrent infections.

Chickenpox is of particular concern since this may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes

zoster and if exposed they should seek urgent medical attention. Passive immunization is recommended for non-immune patients who do come into contact with chickenpox. If a diagnosis of chickenpox is confirmed the illness warrants specialist care and urgent treatment.

Live vaccines are contraindicated in individuals on high doses of corticosteroids and should be postponed until at least 3 months after stopping corticosteroid therapy.

Ocular Effects

Prolonged use of corticosteroids may produce subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves.

Corticosteroids should only be initiated in patients with ocular herpes simplex with appropriate viral cover by ophthalmologists because of the risk of corneal scarring loss of vision and corneal perforation.

Psychiatric effects

Patients and/or carers should be warned that potentially severe psychiatric reactions may occur. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients and/or carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Particular care is required when considering the use of prednisone in patients with existing or previous history of severe affective disorders.

Psychic derangements range from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations.

Use in Pregnancy and Lactation

Category A

Prednisone crosses the placenta and although there have been reports of foetal abnormalities in animal studies these findings do not seem to be relevant to humans. Use in pregnancy requires that the possible benefit to the mother be weighed against the potential hazards to the foetus.

Corticosteroids appear in breast milk but physiologic doses of 5mg or less of Prednisone per day are not considered likely to affect the infant adversely. However, the use of higher doses could suppress growth, interfere with endogenous corticosteroid production or cause other unwanted effects and is therefore not recommended.

Use in Children

Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible and therefore long-term administration of pharmacological doses should be avoided. If prolonged therapy is necessary, treatment should be limited to the minimum suppression of the hypothalamo-pituitary adrenal axis and growth retardation, the growth and development of infants and children should be closely monitored. Treatment should be administered where possible as a single dose on alternate days.

Children are at special risk from raised intracranial pressure.

Use in the Elderly

Long-term use in the elderly should be planned bearing in mind the more serious consequences of the common side-effects of prednisone in old age, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close medical supervision is required to avoid life threatening reactions.

Adverse Effects

Adverse effects are generally related to dose and duration of treatment. Their incidence increases steeply if dosage exceeds 7.5mg prednisone daily.

Body as a whole: leucocytosis, hypersensitivity including anaphylaxis, thromboembolism, fatigue, malaise

Cardiovascular: congestive heart failure in susceptible patients, hypertension

Gastro-intestinal: dyspepsia, nausea, peptic ulceration with perforation and haemorrhage, abdominal distension, abdominal pain, increased appetite which may result in weight gain, diarrhoea, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis

Musculoskeletal: proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, myalgia

Metabolic/Nutritional: sodium and water retention, hypokalaemic alkalosis, potassium loss, negative nitrogen and calcium balance

Skin: impaired healing, hirsutism, skin atrophy, bruising, striae, telangiectasia, acne, increased sweating, may suppress reactions to skin tests, pruritis, rash, urticaria

Endocrine: suppression of the hypothalamo-pituitary adrenal axis particularly in times of stress as in trauma surgery or illness, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, manifestation of latent diabetes mellitus, increased appetite.

Nervous system: euphoria, psychological dependence, depression, insomnia, dizziness, headache, vertigo, raised intracranial pressure with papilloedema in children, usually after treatment withdrawal. Aggravation of schizophrenia, Aggravation of epilepsy suicidal ideation, mania, delusions, hallucinations, irritability anxiety, insomnia and cognitive dysfunction. In adults the frequency of severe psychiatric reactions has been estimated to be 5-6%.

Eye disorders: increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease

Anti-inflammatory and Immunosuppressive effects: increased susceptibility to and severity of infections with suppression of clinical symptoms and signs. Opportunistic infections, recurrence of dormant tuberculosis.

Withdrawal symptoms : too rapid a reduction of prednisone following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. A steroid withdrawal syndrome seemingly unrelated to adrenocortical insufficiency may also occur and include symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, weight loss, and/or hypotension. Also refer to the *Warning and Precautions* section.

Interactions

Hepatic microsomal enzyme inducers

Medicines that induce hepatic enzyme cytochrome P-450 isozyme 3A4 such as Phenobarbital, phenytoin, rifampicin, rifabutin, carbamazepine, primidone and aminogluethimide may reduce the therapeutic efficacy of corticosteroids by increasing the rate of metabolism.

Hepatic microsomal enzyme inhibitors

Medicines that inhibit hepatic enzyme cytochrome P-450 isozyme 3A4 such as ketoconazole, ciclosporin or ritonavir may decrease glucocorticoid clearance. A reduction in prednisone dose may be needed to reduce the risk of adverse effects.

Antidiabetic Agents

Prednisone may increase blood glucose levels. Patients may need dosage adjustment of any concurrent antidiabetic therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Concomitant administration may increase the risk of GI ulceration. Aspirin should be used cautiously in conjunction with prednisone in patients with hypothrombinaemia. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Patients should be observed closely for adverse effects of either medicine.

Anticoagulants

Response to anticoagulants may be reduced or less often enhanced by corticosteroids. Close monitoring of the INR or prothrombin time is recommended.

Antifungals

The risk of hypokalaemia may be increased with amphotericin.

Cardiac glycosides

There is a risk of toxicity if hypokalaemia occurs due to prednisone treatment.

Cytotoxic agents

There is an increased risk of haematological toxicity when prednisone is given with methotrexate.

Mifepristone

The effect of corticosteroids may be reduced for 3-4 days after mifepristone.

Vaccines

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

Oestrogens

Oestrogens may potentiate the effects of glucocorticoids. The dose of prednisone may need to be adjusted if oestrogen therapy is commenced or stopped.

Somatropin

The growth promoting effect may be inhibited.

Sympathomimetics

There is an increased risk of hypokalaemia if high doses of corticosteroids are given with high doses of salbutamol, salmeterol, terbutaline or formoterol.

Diuretics

Excessive potassium loss may be experienced if glucocorticoids and potassium-depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide) are given together.

Antacids

Concurrent use of antacids with prednisone may decrease absorption of these glucocorticoids – efficacy may be decreased sufficiently to require dosage adjustments in patients receiving small doses of prednisone.

Overdosage

Acute overdosage is unlikely to cause any life threatening symptoms and treatment is rarely necessary.

Pharmaceutical Precautions

Shelf life: 24 Months from date of manufacture.

Store at or below 30°C. Protect from heat, light and moisture.

Keep container tightly closed.

Medicine Classification

Prescription Only Medicine

Package Quantities

APO-PREDISONE 1mg tablets:
Bottles of 100 and 500 tablets

APO-PREDISONE 2.5mg tablets:
Bottles of 100 and 500 tablets

APO-PREDISONE 5mg tablets:
Bottles of 100 and 500 tablets

APO-PREDISONE 20mg tablets:
Bottles of 100 and 500 tablets

Further Information

APO-PREDNISONE 1mg and 2.5mg tablets contain lactose and corn starch.

APO-PREDNISONE 5mg and 20mg tablets contain lactose.

APO-PREDNISONE 20mg tablets contain FD&C Red No. 3 as colourant.

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