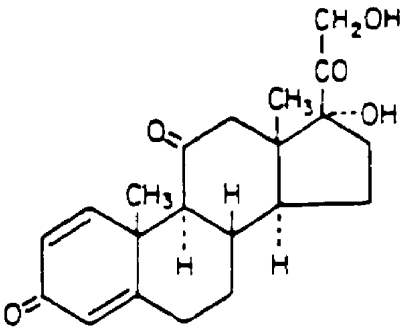
PRODUCT INFORMATION

PRODUCT NAME: SONE

NAME OF THE MEDICINE.
Prednisone.
Structural formula:



Chemical name: 17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione
Cas No. 53-03-2

DESCRIPTION

Prednisone occurs as white to practically white, odourless, crystalline powder. Prednisone is very slightly soluble in water, slightly soluble in alcohol, in chloroform, in dioxane, and in methanol. Prednisolone is very slightly soluble in water and sparingly soluble in alcohol.

Sone tablets contain the following excipients; Lactose, propyl hydroxybenzoate, gelatin, starch-maize, starch-wheat and magnesium stearate.

PHARMACOLOGY

Prednisone is a synthetic corticosteroids with glucocorticoid and anti-inflammatory effects. Prednisone has the same chemical relationship to prednisolone as cortisone has to hydrocortisone. Prednisolone exceeds hydrocortisone in glucocorticoid and anti-inflammatory activity, being about three times **more potent on a weight** basis than the parent hormone, but is considerably less active than hydrocortisone in mineralocorticoid activity.

Prednisolone like hydrocortisone is a potent therapeutic agent influencing the biochemical behaviour of most tissues of the body.

The mechanism of action of corticosteroids is thought to be by control of protein synthesis. Corticosteroids react with receptor proteins in the cytoplasm of sensitive cells in many tissues to form a steroid-receptor complex.

Corticosteroids are palliative symptomatic treatment by virtue of their anti-inflammatory effects; they are never curative.

Pharmacokinetics: Prednisone is readily absorbed from the gastrointestinal tract, but must be converted in the liver to its active metabolite, prednisolone.

Absorption: The plasma half-life after oral administration of prednisone ranges from 3 to 4 hours. Oral bioavailability varies widely between subjects. With the active metabolite prednisolone, peak plasma concentrations are obtained 1 or 2 hours after oral administration and prednisolone has a usual plasma half-life of 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food.

Distribution: Prednisolone is 90 to 95% bound to plasma proteins.

Metabolism: The conversion from prednisone into prednisolone is rapid so that prednisone has a pre-conversion biological half life of only about 60 minutes. Prednisolone is conjugated in the liver and to some extent in the kidney.

Excretion: Little prednisone is excreted unchanged in the urine, however prednisolone is excreted in the urine as free and conjugated metabolites, together with an appreciable proportion of unchanged prednisolone. Prednisolone crosses the placenta and small amounts are excreted in breast milk.

INDICATIONS

Wherever corticosteroid therapy is indicated.

CONTRAINDICATIONS

Systemic fungal infections and known hypersensitivity to prednisone or any of the excipients.

Peptic ulcer, osteoporosis, psychoses or severe psychoneuroses. Patients with active or doubtfully quiescent tuberculosis should not be given these hormones except as adjuncts to treatment with tuberculostatic drugs.

PRECAUTIONS

Corticosteroids should be used with caution in the presence of diminished cardiac reserve or congestive heart failure, in patients with diabetes mellitus, infectious diseases, chronic renal failure, uraemia and in elderly persons.

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. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. 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.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox 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. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

Withdrawal symptoms

During prolonged treatment with corticosteroids, adrenal suppression and atrophy may occur and secretion of corticotrophin may be suppressed. Sudden withdrawal of the hormone treatment may then precipitate acute adrenal insufficiency with muscle weakness, hypotension, hypoglycaemia, headache, nausea, vomiting, restlessness and muscle and joint pain. Muscle weakness and stiff joints may persist for three to six months after treatment has been discontinued. In some instances, withdrawal symptoms may stimulate a clinical relapse of the disease for which the patient has been under treatment. Duration of treatment and dosage appear to be important factors in determining suppression of the pituitary adrenal axis and response to stress on cessation of steroid treatment. Individual liability to depression is also variable. Some patients may recover normal function rapidly. In others, the production of hydrocortisone in response to the stress of infections, surgical operations or accident may be insufficient, and death results. Withdrawal of corticosteroids should therefore always be gradual but if sudden withdrawal is necessary, corticotrophin (20 units) given daily by intravenous infusion over eight

hours for three to five successive days is usually sufficient to prevent withdrawal symptoms.

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 is possible, 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.

Steroids should be used with caution in non-specific 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.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

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

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Carcinogenicity/mutagenicitv

In male rats, administration of prednisolone in the drinking water at a daily dose level of 0.4mg/kg for two years caused an increased incidence of hepatocellular tumours. Similar results were obtained with triamcinolone acetonide and budesonide, indicating a class effect of glucocorticosteroids. The hepatocarcinogenic response to these drugs does not appear to be related to genotoxic activity.

The carcinogenic potential of prednisone has been evaluated in mice at oral doses up to 5mg/kg/day for 18 months. No carcinogenic effect was noted in the mouse.

Use in pregnancy. (Category A)
In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations) and abortion. These findings do not seem to be relevant to humans. Reduced placental and birth weight have been recorded in animals and humans after long term treatment. Since the possibility of suppression of the adrenal cortex in the newborn infant after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the fetus when prescribing these drugs. The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the fetus or the newborn infant. Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

Use in lactation
The drug is excreted in breast milk; therefore, administration to nursing mothers is not recommended.

INTERACTIONS WITH OTHER MEDICINES

The following drug interactions with corticosteroids have been selected on the basis of their potential clinical significance: antacids, antidiabetic agents (oral or insulin), digitalis glycosides, diuretics, drugs which induce hepatic microsomal enzymes, such as barbiturates, phenytoin and rifampicin; potassium supplements, ritodrine, sodium-containing medications or foods, somatrem or somatropin, vaccines, live viruses or other immunizations.

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 clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.

The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

Effects on Laboratory tests
Glucocorticoids may decrease I^{131} uptake and protein-bound iodine concentrations, making it difficult to monitor the therapeutic response of patients receiving the drugs for thyroiditis. Glucocorticoids may produce false-negative results in the nitroblue tetrazolium test for systemic bacterial infection. Glucocorticoids may suppress reactions to skin tests.

ADVERSE EFFECTS

The side effects associated with the use of corticosteroids in the large doses necessary to produce a therapeutic response result from excessive action on electrolyte balance: excessive action on other aspects of metabolism including gluconeogenesis; the action on tissue repair and healing; and an inhibitory effect on the secretion of corticotrophin by the anterior pituitary gland. Disturbance of electrolyte and water balance is manifest in sodium retention with oedema and hypertension, and in the increased excretion of potassium with the development of hypokalaemic alkalosis. In extreme cases cardiac failure may be induced. Disturbances of electrolyte balance are common with the naturally occurring corticotrophins, cortisone, deoxycortone and hydrocortisone but are less frequent with the synthetic derivatives, prednisone and prednisolone. Other metabolic effects include mobilisation of calcium and phosphorus with osteoporosis and spontaneous fractures; nitrogen depletion and hyperglycaemia with accentuation or precipitation of the diabetic state. The insulin requirements of diabetic patients are increased and appetite is often increased.

The effect on tissue repair manifests as peptic ulceration with haemorrhage and perforation, delayed wound healing and increased liability to infection. Increased susceptibility to all kinds of infection, including sepsis, fungal and viral infection, has been reported.

Large doses of corticosteroids or corticotrophins may produce symptoms typical of hyperactivity of the adrenal cortex, with moonface, buffalo hump, flushing striae and acne sometimes leading to a fully developed Cushing's syndrome. If administration of the hormone is discontinued immediately on the appearance of these symptoms, they are usually reversed but such sudden cessation may be dangerous. The dose of corticosteroid required to cause a decrease or absence of corticotrophin in the blood with consequent atrophy of the adrenal cortex and the time required for its occurrence are very variable. Acute adrenal insufficiency with loss of consciousness may occur during prolonged treatment or on cessation of treatment and may be precipitated by an infection or trauma.

Growth retardation in children has been reported and in this respect cortisone is only one-tenth as potent as prednisone and prednisolone. Other toxic effects include mental and neurological disturbances, intracranial hypertension and, on sudden reduction of dosage during the treatment of rheumatoid arthritis, fatalities attributed to lesions of small arteries and arterioles similar to polyarteritis.
Infections may be masked since corticosteroids have marked anti-inflammatory and antipyretic properties and may produce a feeling of well-being. The administration of corticosteroids may also cause a reduction in the number of circulating lymphocytes.

Muscular weakness is an occasional side effect of most corticosteroids, particularly when they are taken in large doses.

Toxic effects occur with all corticosteroid preparations and their incidence rises steeply if dosage increases much above 8 mg daily of prednisolone or its equivalent.

FLUID AND ELECTROLYTE DISTURBANCES
Sodium retention
Fluid retention
Congestive heart failure in susceptible patients. Potassium loss
Hypokalemic alkalosis
Hypertension

MUSCULOSKELETAL
Muscle weakness
Steroid myopathy
Loss of muscle mass
Osteoporosis
Tendon rupture, particularly of the Achilles tendon
Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

GASTROINTESTINAL
Peptic ulcer with possible perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative oesophagitis
Increases in alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

DERMATOLOGIC
Impaired wound healing
Thin fragile skin
Petechiae and ecchymoses
Facial erythema
Increased sweating. May suppress reactions to skin tests

METABOLIC
Negative nitrogen balance due to protein catabolism

NEUROLOGICAL
Increased intracranial pressure with papilloedema (pseudo-tumour cerebri) usually after treatment
Convulsions
Vertigo
Headache

ENDOCRINE
Menstrual irregularities
Development of Cushingoid state
Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress as in trauma, surgery or illness. Suppression of growth in children
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements for insulin or oral hypoglycaemic agents in diabetics

OPHTHALMIC
Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos

ADDITIONAL REACTIONS
Urticaria and other allergic, anaphylactic or hypersensitivity reactions

DOSAGE AND ADMINISTRATION

Adults: 10 to 100 mg daily in divided doses.
Children: 1 to 5 years. 2.5 to 10 mg twice daily. 6 to 12 years: 5 to 20 mg twice daily.

OVERDOSAGE

Treatment There is no specific antidote Toxic effects are signs of overdosage, and should be treated symptomatically and dosage reduced or the drug withdrawn. During long courses of treatment laboratory and metabolic studies should be made. Fluid retention should be watched for via a fluid balance chart and daily weighing. Sodium intake may need to be reduced to less than 1g daily and potassium supplements may be necessary.

PRESENTATION AND STORAGE CONDITIONS

Sone Tablets, 5 mg (white, scored): 60's; 25 mg (white, scored): 30's.
Storage: Store below 30°C. Protect from light. Shelf life: 3 years.

NAME AND ADDRESS OF THE SPONSOR

iNova Pharmaceuticals (Australia) Pty Ltd
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Chatswood, NSW 2067
Australia

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS: 26 March 1997.

Date of most recent amendment: 26 June 2013.