APPROVED PRODUCT INFORMATION

CORTATE

NAME OF THE DRUG:

Cortisone acetate.
Chemical name: 21-(acetyloxy)-17-hydroxypregn-4-ene-3,11,20-trione
Empirical formula: C_{23}H_{30}O_{6} Molecular weight: 402.49
Chemical structure:

[CAS:50-04-4]

DESCRIPTION:

Cortisone acetate is a white or practically white, odourless, crystalline powder. It is stable in air and is insoluble in water.

Cortate 5mg tablets are round, flat, white tablets. Excipients used in Cortate 5mg tablets include lactose, macrogol 6000, povidone, magnesium stearate and starch-maize.

Cortate 25mg tablets are round, flat, white, scored tablets. Excipients used in Cortate 25mg include lactose, povidone, magnesium stearate and starch-maize.

ACTIONS:

Mineralocorticoid and glucocorticoid. Naturally occurring glucocorticoids such as hydrocortisone and cortisone which also have salt-retaining properties are used as replacement therapy in adrenocortical deficiency states. They are also used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body’s immune response to diverse stimuli.

PHARMACOKINETICS:

Cortisone is inactive until the 11-oxo group is reduced by 11-ß-hydroxy-dehydrogenase to form the active product, hydrocortisone (or cortisol). The relative bioavailability of cortisone compared to hydrocortisone is approximately 80%, with the difference being attributed to a small amount of metabolism of cortisone to the inactive, tetrahydrocortisone.

The biological half life of hydrocortisone is about 100 minutes and it is more than 90% bound to plasma proteins. The main elimination route of hydrocortisone is by metabolism to tetrahydrocortisone. There is little conversion of hydrocortisone back to cortisone. Tetrahydrocortisone and tetrahydrocortisonl are excreted in the urine, mainly conjugates as glucuronides, together with a very small proportion of unchanged hydrocortisone.
In patients, with cirrhosis, the conversion of cortisone to hydrocortisone is preserved but the half life of hydrocortisone is prolonged markedly to around 5 hours. In patients with thyrotoxicosis, there is a greater rate of conversion for cortisone to hydrocortisone and a shortened half life of hydrocortisone to around 1 hour.

**INDICATIONS:**

Addison’s disease; allergic disorders including status asthmaticus; angioneurotic oedema, serum sickness and drug sensitisation; periarteritis nodosa; disseminated lupus erythematosus; giant cell arteritis.

**CONTRAINDICATIONS:**

Hypersensitivity to cortisone acetate or any ingredients listed in the “Description” section, uncontrolled infections.

**PRECAUTIONS:**

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.

Patients, including those with Addison’s disease, should be observed closely for signs that may require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (eg. surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

During prolonged corticosteroid therapy, adrenal suppression and atrophy may occur and secretion of corticotrophin may be suppressed. 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. The patient's liability to suppression 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. Therefore, withdrawal of corticosteroids should always be gradual.

Abrupt withdrawal of corticosteroid therapy may precipitate acute adrenal insufficiency (see ADVERSE REACTIONS). In some cases, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been under treatment.

**Use with caution in the following circumstances:**

Use with caution in patients with impaired hepatic function, as a reduction of dosage may be necessary. In treating chronic active liver disease with the drug, major adverse reactions such as vertebral collapse, diabetes, hypertension, cataracts and Cushing's syndrome occur in about 30% of patients.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diverticulitis, recent intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension and myasthenia gravis, when steroids are used as direct or adjunctive therapy.
Use with caution in patients with epilepsy, diabetes mellitus, uraemia and in the presence of diminished cardiac reserve, congestive heart failure or thromboembolic disorders. (see ADVERSE REACTIONS).

The possibility of development of osteoporosis should be an important consideration in initiating and managing corticosteroid therapy, especially in post menopausal women (see ADVERSE REACTIONS).

The risk of gastrointestinal ulceration or hemorrhage is increased when alcohol is used concurrently with glucocorticoids.

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.

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

Use with caution in patients with emotional instability or psychotic tendencies.

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

Infection: Corticosteroids may mask some signs of infection (such as fever and inflammation), and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. Susceptibility to infection is not specific for any particular bacterial or fungal pathogen.

Patients should not be vaccinated with live vaccines while on corticosteroid therapy. Other immunisation procedures should not be undertaken in patients on corticosteroid therapy, especially on high doses, because of possible hazards of neurological complications and lack of antibody response. Immunization procedures may be undertaken in patients receiving corticosteroids as replacement therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Patients with active or doubtfully quiescent tuberculosis should not be given CORTATE except as adjuncts to treatment with tuberculostatic drugs as reactivation of the disease may occur. Chemoprophylaxis is indicated during prolonged corticosteroid therapy.

Kaposi’s sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
Check the following during use:

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 1 g daily and potassium supplements may be necessary.

Use in Children

Children on long term steroids must be carefully observed for potential serious adverse reactions such as obesity, growth retardation, osteoporosis and adrenal suppression.

Use in Elderly

Caution is recommended for elderly patients as they are more susceptible to adverse reactions.

Carcinogenicity/Mutagenicity

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. 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.

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 baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the fetus when prescribing corticosteroids. 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 newborn infant.

Corticosteroids may be associated with tocolysis (inhibition of uterine contraction) and maternal fluid overload.

Use in Lactation

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

Interactions with other drugs:

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, somatropin, vaccines, live viruses or other immunisations.
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 effects associated with the individual use of either drug may be more apt to occur.

Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampicin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response.

Drugs such as ketoconazole may inhibit the metabolism of corticosteroids and thus decreased their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity.

Corticosteroids may 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.

The various CYP450 isozymes responsible for these drug interactions are poorly understood due to the lack of information on the interaction between CYP450 isozymes and corticosteroids.

Antacids, cholestyramine, colestipol – Decrease cortisone’s effect by adsorbing the corticosteroid, decreasing the amount absorbed. Advise clinican to monitor patient carefully.

Cardiac glycosides – Hypokalaemia may increase the risk of toxicity in patients also receiving cardiac glycosides. Avoid use together.

Diuretic or amphotericin B therapy – Cortisone may enhance hypokalaemia associated with diuretic or amphotericin B therapy. Advise clinican to monitor serum blood levels closely, especially potassium.

Estrogens – May reduce the metabolism of cortisone. The half-life of cortisone is then prolonged. Avoid use together.

Insulin, oral antidiabetics – Cause hyperglycaemia. Dosage adjustment may be needed.

Isoniazid, salicylates – When used together, cortisone increases the metabolism of isoniazid and salicylates. Use together cautiously.

Toxoids, inactivated vaccines – Cortisone may have a diminished response to toxoids or inactivated vaccines. Avoid use together.

Alcohol – Increased risk of gastric irritation and GI ulceration. Advise patient to avoid alcohol.

**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 REACTIONS:

Short-term administration of CORTATE, even in large doses, is unlikely to produce harmful effects. The majority of adverse reactions from corticosteroids are those resulting from withdrawal or from prolonged use of high doses.

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 can manifest as peptic ulceration with haemorrhage and perforation, delayed wound healing and increased liability to infection. Increased susceptibility to all 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 1/10 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 and eosinophils. 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 40mg daily of cortisone or its equivalent.
Postmarketing Reaction Frequencies

(>5%)

**Gastrointestinal:** Increased appetite; indigestion

**Neurological:** Nervousness or restlessness; insomnia

(1-5%)

**Dermatological:** Local allergic reaction

**Gastrointestinal:** Pancreatitis and ulcerative oesophagitis can occur. Peptic ulceration is an occasional complication. The high incidence of haemorrhage and perforation in these ulcers and the insidious nature of their development make them severe therapeutic problems. Some investigators believe the available evidence does not support the conclusion that steroids cause ulcers. Others feel that only patients with rheumatoid arthritis have an increased incidence of ulcers. It has been proposed that the glucocorticoids alter the mucosal defence mechanism.

**Ophthalmological:** Prolonged use of glucocorticoids may result in posterior subcapsular cataracts (particularly in children), exophthalmos, or increased intraocular pressure which may result in glaucoma or may occasionally damage the optic nerve and in rare cases, lead to blindness. Establishment of secondary fungal and viral infections of the eye may also be enhanced.

**Biochemical:** All glucocorticoids increase gluconeogenesis. Glucose tolerance and sensitivity to insulin are decreased but provided pancreatic islet function is normal carbohydrate metabolism may not be significantly deranged. Steroid-induced diabetes, has been reported to develop in one fifth of patients treated with high glucocorticoid dosage. High dose corticosteroid therapy may induce marked hypertriglyceridaemia with milky plasma.

(<1%)

**Dermatological:** Dermatological adverse effects of corticosteroids include impaired wound healing, facial plethora, increased sweating, easy bruising, hirsutism, an acneiform eruption on the face, chest and back, red striae on the thighs, buttocks and shoulders. Several months of high dose therapy can often result in thinning of skin. Dermatologic manifestations of hypersensitivity to the corticosteroids include hives and/or allergic dermatitis, urticaria, and angioedema. Corticosteroid induced purpura resembles senile purpura. This purpura usually occurs on extensor surfaces, dorsum of the hand, and radial aspect of the forearm.

**Neurological:** Adverse neurological effects have included headache, vertigo and increased motor activity, ischemic neuropathy, EEG abnormalities and seizures. Large doses can cause behavioural and personality changes ranging from nervousness, euphoria or mood swings to psychotic episodes which can include both manic and depressive states, paranoid states and acute toxic psychoses.

It is no longer believed that previous psychiatric problems predispose to behavioural disturbances during therapy with glucocorticoids. Conversely, the absence of a history of psychiatric illness is no guarantee against the occurrence of psychosis during hormonal therapy.

Pseudomotor cerebri and paresthesia have also been reported.
**Endocrine:** The endocrine effects of the glucocorticoids involve variously the hypothalamic pituitary adrenal axis; the parathyroid and thyroid. There are also metabolic effects, primarily involving the carbohydrates. Suppression of growth may occur in children. Cushing's syndrome may result from prolonged elevation of plasma glucocorticoid levels. Corticosteroids have also been reported to increase or decrease motility and number of sperm in some men. Disorders of menstruation are common.

Antagonism occurs between the parathyroids and hypercorticism. Latent hypoparathyroidism may be unmasked by administration of corticosteroids. The phosphate retention occurring in renal failure caused by adrenal insufficiency may also make hypoparathyroidism manifest.

Hypocalcaemia, hypercholesterolemia, decreased serum thyroxine and triiodothyronine levels have also been reported.

**Gastrointestinal:** Adverse gastrointestinal effects of corticosteroids include nausea, vomiting, anorexia (which may result in weight loss), diarrhoea or constipation, abdominal distension and gastric irritation.

**Cardiovascular:** The mineralocorticoid activity of a steroid may lead to salt and water retention which can also result in hypertension. Hypokalaemia can lead to arrhythmias and cardiac arrest. Heart failure, thromboembolism and thrombophlebitis have also been reported.

**Musculoskeletal:** Osteoporosis and vertebral compression fractures can occur in patients of all ages. Osteoporosis is an indication for withdrawal of therapy. Myopathy, characterised by weakness of the proximal musculature of arms and legs and their associated shoulder and pelvic muscles, is occasionally reported in patients taking large doses of corticosteroids. It may occur soon after treatment is begun and be sufficiently severe to prevent ambulation. It is an indication for withdrawal of therapy. Avascular aseptic necrosis of bone has often been described and preferentially involves the femoral and humeral head.

**Withdrawal Adverse Effects**

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 discontinuation of treatment. Adverse reactions from corticosteroids are those resulting from withdrawal or from prolonged use of high doses.

In patients who have received systemic corticosteroids for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may therefore be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 7.5mg of prednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover.

The following adverse reactions have also been reported, however, there is no information on their incidences.

**General:** Retardation of growth by long term corticosteroid treatment in children.

**Haematological:** Corticosteroids will increase the total WBC count, with an increase in neutrophils and a decrease in monocytes, lymphocytes and eosinophils.
Immunological: The frequency and severity of clinical infections increase during glucocorticoid therapy.

Serious or Life Threatening Reactions
Suppression of the hypothalamic pituitary adrenal axis is one of the consequences of repeated administration of glucocorticoids (see PRECAUTIONS). In some cases acute adrenal insufficiency after a period of glucocorticoid treatment has proved fatal.

Neurological: Latent epilepsy can be rendered manifest by corticosteroid treatment. Long term treatment may result in benign intracranial hypertension.

DOSAGE & ADMINISTRATION:
Dosage requirements are variable and must be individualised on the basis of the disease and the response of the patient. 25 mg once every 6 hours for an adult may be used to initiate treatment. Once remission is achieved, the daily dosage is reduced by 10 to 20 mg every few days until the optimum maintenance dose results. Acute and severe sensitivity or anaphylactic states may require much larger doses.

OVERDOSAGE:
Acute ingestion, even in massive doses, is rarely a clinical problem. Toxic signs and symptoms rarely occur if the drug is used for less than 3 weeks, even at large dosage ranges. However, chronic use causes adverse physiologic effects.

Immediately telephone the Poisons Information Centre for advice on 13 11 26.

PRESENTATION:
Tablets
5mg: 50's; 25mg: 30's, 60's.

SPONSOR:
Aspen Pharmacare Australia Pty Ltd
3/34-36 Chandos St
St Leonards NSW 2065
Australia

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