SOLU-CORTEF®

hydrocortisone sodium succinate
Powder for Injection, 100 mg Act-O-Vial

PRESENTATION

SOLU CORTEF is a white or nearly white odourless, hygroscopic amorphous solid, available in Act-O-Vials containing hydrocortisone sodium succinate as the active ingredient, equivalent to 100 mg hydrocortisone when mixed with 2 mL of sterile Water for Injections. It also contains 0.8 mg sodium phosphate monobasic (anhydrous) and 8.73 mg of sodium phosphate dibasic (anhydrous).

USES

Actions

Hydrocortisone sodium succinate is an anti-inflammatory adrenocortical steroid. This highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly.

Pharmacokinetics

Absorption

Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. This preparation is also rapidly absorbed when administered intramuscularly. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours.

Biotransformation or Metabolism

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory action as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity.

Elimination

Excretion of the intravenous administered dose is nearly complete within 12 hours. Intramuscular injections are excreted in a pattern similar to that observed after intravenous injections.
INDICATIONS

Endocrine Disorders

- Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)

- Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)

- Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful

- Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected

- Congenital adrenal hyperplasia

- Hypercalcaemia associated with cancer

- Nonsuppurative thyroiditis.

Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- post-trauma osteoarthritis

- epicondylitis

- synovitis or osteoarthritis

- acute nonspecific tenosynovitis

- rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

- acute and subacute bursitis

- acute gouty arthritis

- psoriatic arthritis

- ankylosing spondylitis
**Collagen Diseases**
During an exacerbation or as maintenance therapy in selected cases of:
- systemic lupus erythematosus
- acute rheumatic carditis
- systemic dermatomyositis (polymyositis).

**Dermatologic Diseases**
- pemphigus
- severe erythema multiforme (Stevens-Johnson Syndrome)
- exfoliative dermatitis
- bullous dermatitis herpetiformis
- severe seborrhoeic dermatitis
- severe psoriasis
- mycosis fungoides

**Allergic States**
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
- bronchial asthma
- contact dermatitis
- atopic dermatitis
- serum sickness
- seasonal or perennial allergic rhinitis
- drug hypersensitivity reactions
- urticarial transfusion reactions
- acute noninfectious laryngeal
- oedema (epinephrine is the drug of first choice).

**Ophthalmic Diseases**
Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
- herpes zoster ophthalmicus
- iritis, iridocyclitis
- chorioretinitis
- diffuse posterior uveitis and choroiditis
- optic neuritis
- sympathetic ophthalmia
- anterior segment inflammation
- allergic conjunctivitis
- allergic corneal marginal ulcers
- keratitis.

**Gastrointestinal Diseases**
To tide the patient over a critical period of the disease in:
- ulcerative colitis (systemic therapy)
- regional enteritis (systemic therapy)

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

**Haematologic Disorders**
- acquired (autoimmune) haemolytic anaemia
- idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)
- secondary thrombocytopenia in adults
- erythroblastopenia (RBC anaemia)
• congenital (erythroid) hypoplastic anaemia.

Neoplastic Diseases
For palliative management of:
• leukaemias and lymphomas in adults
• acute leukaemia of childhood.

Oedematous States
To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uraemia, or the idiopathic type or that due to lupus erythematosus.

Nervous System
Acute exacerbations of multiple sclerosis.

Medical Emergencies
SOLU-CORTEF is indicated in the treatment of:
• Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present
• Acute allergic disorders (status asthmaticus, anaphylactic reactions, insect stings, etc.) following epinephrine.
• Although there are no well controlled (double-blind, placebo) clinical trials, data from experimental animal models indicate that corticosteroids may be useful in haemorrhagic, traumatic and surgical shock in which standard therapy (e.g. fluid replacement etc) has not been effective.

Miscellaneous
• Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
• Trichinosis with neurologic or myocardial involvement.

DOSAGE AND ADMINISTRATION

Since complications of treatment with corticosteroids 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.

The lowest possible dose should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.
SOLU-CORTEF may be administered by intravenous injection, by intravenous infusion, or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Therapy is initiated by administering SOLU-CORTEF Sterile powder intravenously over a period of 30 seconds (e.g. hydrocortisone sodium succinate equivalent to 100 mg of hydrocortisone) to 10 minutes (e.g. 500 mg or more). In general, high-dose corticosteroid therapy should be continued only until the patient's condition has stabilised - usually not beyond 48 to 72 hours. Although adverse effects associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

When high-dose hydrocortisone therapy must be continued beyond 48-72 hours, hypernatremia may occur. Under such circumstances it may be desirable to replace SOLU-CORTEF with a corticoid product such as one containing methylprednisolone sodium succinate which causes little or no sodium retention.

The initial dose of SOLU-CORTEF is 100 mg to 500 mg or more (hydrocortisone equivalent of hydrocortisone sodium succinate) depending on the severity of the condition.

This dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient's responses and clinical condition. While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily.

Patients subjected to severe stress following corticosteroid therapy should be observed closely for signs and symptoms of adrenocortical insufficiency.

Corticosteroid therapy is an adjunct to, and not a replacement for, conventional therapy.

**Dosage Adjustment in Hepatic Impairment**

In patients with liver disease, there may be an increased effect of hydrocortisone resulting from decreased metabolism and elimination of the drug. Monitoring the clinical response to hydrocortisone in these patients should be considered (see **WARNINGS AND PRECAUTIONS**).

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**CONTRAINDICATIONS**

Systemic infections unless specific anti-infective therapy is given.

Known hypersensitivity to the drug or any component of the formulation.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

SOLU-CORTEF (hydrocortisone sodium succinate) is not indicated for intrathecal, epidural or local injection, or any other unspecified route of administration.
WARNINGS AND PRECAUTIONS

Immunosuppressive Effects/Increased Susceptibility to Infections

Due to their suppression of the inflammatory response and immune function, corticosteroids may increase susceptibility to fungal, bacterial and viral infections and their severity. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. How the dose, route and duration of corticosteroid administration affect 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. If exposed to chicken pox, they should seek urgent medical attention. Passive immunisation is recommended if non-immune patients who come into contact with chicken pox. If a diagnosis of chicken pox is confirmed the illness warrants specialist care and urgent treatment.

The immunosuppressive effects of corticosteroids may also result in activation of latent infection or exacerbation of existing infection. Corticosteroids should be used with great care in patients with known or suspected parasitic infections such as Strongyloides infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicaemia.

It is important to note that corticosteroids may also mask some signs of infection which may reach an advanced stage before the infection is recognised.

There may also be decreased resistance and inability to localize infection when corticosteroids are used.

Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in 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.

Although recent studies have not been conducted with hydrocortisone or other corticosteroids, studies of methylprednisolone sodium succinate in septic shock suggest that increased mortality may occur in some subgroups of patients at higher risk (i.e., elevated creatinine greater than 2.0 mg% or with secondary infections). Therefore, SOLU-CORTEF is not recommended for use in patients with septic shock or sepsis syndrome.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids and should be postponed until at least three months after stopping corticosteroid therapy. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.
The use of corticosteroids 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.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

**Endocrine**

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 corticosteroid 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.

Drug-induced adrenocortical insufficiency may be minimised by reduction of dosage, however symptoms may persist for months after discontinuation of corticosteroid therapy. It is important to note that acute adrenal insufficiency leading to a fatal outcome may occur if corticosteroids are withdrawn abruptly. Therefore, withdrawal of corticosteroids should always be gradual.

In patients on corticosteroid therapy (or those who have discontinued treatment but continue to experience symptoms of adrenal insufficiency) who are subjected to unusual stress such as intercurrent illness, trauma or surgery, increased dosage (or reinstitution) of rapidly acting corticosteroids may be required.

A steroid “withdrawal syndrome”, seemingly unrelated to adrenocortical insufficiency, may occur following abrupt discontinuance of corticosteroids. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see ADVERSE EFFECTS, General disorders and administration site conditions).

Because corticosteroids can produce or aggravate Cushing’s syndrome, they should be avoided in patients with Cushing’s disease.

Corticosteroids should be used with caution in patients with hypothyroidism as there is potential for an enhanced effect of corticosteroids in these patients.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.
**Metabolism and Nutrition**

Corticosteroids can increase blood glucose, worsen pre-existing diabetes and predisposes those on long term corticosteroid therapy to diabetes mellitus; therefore corticosteroids should be used with caution in patients with, or a family history of, diabetes mellitus.

Hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium and calcium supplementation may be necessary. All corticosteroids increase calcium excretion.

**Psychiatric**

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. Therefore, particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

Symptoms of potentially severe psychiatric adverse reactions associated with corticosteroid use 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. Psychological effects have also been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

**Nervous System**

Corticosteroids should be used with caution in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (also see myopathy statement in *Musculoskeletal Effects*).

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 (see **DOSAGE AND ADMINISTRATION**).

There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

**Ophthalmic**

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible risk of corneal scarring, loss of vision and corneal perforation.
Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure may result in glaucoma with possible damage to the optic nerves.

Establishment of secondary ocular infections due to fungi or viruses of the eye may also be enhanced in patients receiving corticosteroids.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

**Cardiac Effects**
Corticosteroids should used with caution, and only if strictly necessary, in patients with congestive heart failure.

**Vascular Effects**
Thrombosis, including venous thromboembolism, has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

**Blood and Lymphatic System**
Aspirin should be used cautiously in conjunction with corticosteroids.

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

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, or active or latent peptic ulcer, oesophagitis and gastritis.

**Hepatobiliary**
Corticosteroids should be used with caution in patients with hepatic failure.

There is an enhanced effect of corticosteroids on patients with cirrhosis.

Hydrocortisone may have an increased effect in patients with liver disease since the metabolism and elimination of hydrocortisone is significantly decreased in these patients.

**Musculoskeletal Effects**
Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity. An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g, myasthenia gravis), or in patients receiving concomitant therapy with
anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Corticosteroids should be used with caution in patients with osteoporosis. Osteoporosis is also a common but infrequently recognized adverse effect associated with a long-term use of large doses of corticosteroids.

Corticosteroids should be used with caution in patients with Duchenne’s muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous activities.

Corticosteroids should also be used with caution in patients with previous steroid myopathy.

**Renal and Urinary**
Corticosteroids should be used with caution in patients with renal insufficiency.

**Investigations**
Hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

**Immune System Disorders**
Because rare instances of anaphylactoid reactions (e.g., bronchospasm) 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.

**Injury, Poisoning and Procedural Complications**
Systemic corticosteroids are not indicated for, and should therefore not be used to treat traumatic brain injury. A multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered corticosteroids compared to placebo. A causal association with corticosteroid treatment has not been established.

**Carcinogenicity, Mutagenicity**
There is no evidence that corticosteroids are carcinogenic or mutagenic.

**Effects on Fertility**
Corticosteroids have been shown to impair fertility in animal studies.

**Use in Pregnancy**
The benefits of the use of SOLU-CORTEF in pregnant women and those of childbearing potential should be carefully weighed against any potential risk to the mother and embryo or
fetus. Since there is inadequate evidence of safety in human pregnancy, SOLU-CORTEF should be used in pregnancy only if clearly needed.

Some animal studies have shown that corticosteroids may cause fetal malformations (cleft palate, skeletal malformations) and abortion. Reduced placental and birth weight have also been recorded after long-term maternal treatment along with potential for suppression of the adrenal cortex in newborns.

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 labour and delivery.

**Use in Lactation**

Corticosteroids are excreted in breast milk. Therefore it is recommended that breastfeeding should cease in women who will be or are receiving corticosteroids.

**Paediatric Use**

Corticosteroids may cause growth retardation in infancy, childhood and adolescence. The effects may be irreversible; therefore long-term daily-divided doses of corticosteroids should be avoided in these patients. In infants, children and adolescents, corticosteroid treatment should be administered where possible as a single dose on alternate days for the shortest possible duration.

If prolonged therapy is necessary, growth and development of these patients should be carefully monitored.

Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of other corticosteroids, such as methylprednisolone.

Benzyl alcohol may be added as a bacteriostatic agent to some Water for Injections. Benzyl alcohol has been reported to be associated with a fatal "Gasing Syndrome" in premature infants. This product DOES NOT contain benzyl alcohol.

**Use in the Elderly**

The use of corticosteroids, particularly long-term use, in the elderly should be planned bearing in mind the more serious consequences of the common side effects, especially; osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

**Effects on Ability to Drive and Use Machines**

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as syncope, vertigo, and convulsions are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.
ADVERSE EFFECTS

The adverse effects listed in the table below are typical for all systemic corticosteroids. Their inclusion in this list does not necessarily indicate that the specific event has been observed with SOLU-CORTEF.

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| **Infections and Infestations** | Increased susceptibility to, and severity of, infections  
Infection masked  
Infection (becoming active, including reactivation of tuberculosis)  
Opportunistic infection (with any pathogen, in any location in the body, from mild to fatal) |
| **Blood and lymphatic system disorders** | Leucocytosis                                                                               |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | Kaposi’s sarcoma (has been reported to occur in patients receiving corticosteroid therapy) |
| **Immune system disorders** | Hypersensitivity (including anaphylaxis and anaphylactoid reactions [e.g., bronchospasm, laryngeal oedema, urticaria])  
Suppression of reactions to skin tests |
| **Endocrine disorders** | Cushingoid  
Pituitary-adrenal axis suppression  
Manifestation of latent diabetes  
Steroid withdrawal syndrome |
| **Metabolism and nutrition disorders** | Alkalosis hypokalaemic  
Fluid retention  
Increased appetite (which may result in weight gain)  
Sodium retention  
Glucose tolerance impaired |
| **Psychiatric disorders** | Abnormal behaviour  
Psychic derangements/psychotic manifestations (euphoric mood, insomnia, mood swings, personality change, depression, exacerbation of preexisting affect lability or psychotic behaviour)  
Behavioural disturbances (including irritability, anxiety, insomnia, cognitive dysfunction including confusion and amnesia) |
| **Nervous system disorders** | Convulsions  
Dizziness  
Headache  
Intracranial pressure increased (with papilloedema)  
Benign intracranial hypertension  
Epidural lipomatosis |
| **Eye disorders** | Cataract subcapsular  
Glaucoma  
Exophthalmos  
Central serous chorioretinopathy  
Corneal thinning  
Scleral thinning  
Exacerbation of ophthalmic viral or fungal disease |
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<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>Vertigo</td>
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<td><strong>Cardiac disorders</strong></td>
<td>Cardiac failure congestive (in susceptible patients)</td>
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| **Vascular disorders** | Thrombosis  
Hypertension |
| **Respiratory, thoracic and mediastinal disorders** | Pulmonary embolism  
Gasping Syndrome |
| **Gastrointestinal disorders** | Abdominal distension  
Abdominal pain  
Diarrhoea  
Dyspepsia  
Nausea  
Oesophagitis  
Peptic ulcer (with possible perforation and haemorrhage)  
Pancreatitis  
Gastric haemorrhage  
Intestinal perforation |
| **Skin and subcutaneous tissue disorders** | Ecchymosis  
Hirsutism  
Hyperhidrosis  
Petechiae  
Pruritus  
Rash  
Skin atrophy  
Skin striae  
Urticaria  
Acne  
Telangiectasia  
Hyperpigmentation or hypopigmentation  
Sterile abscess |
| **Musculoskeletal and connective tissue disorders** | Muscular weakness  
Myalgia  
Myopathy  
Avascular osteonecrosis |
### Osteoporosis
- Pathologic fractures
- Growth retardation

### Reproductive system and breast disorders
- Menstruation irregular
- Amenorrhoea

### General disorders and administration site conditions
- Fatigue
- Impaired healing
- Malaise
- Injection site reaction

### Investigations
- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood alkaline phosphatase increased
- Blood potassium decreased
- Urine calcium increased
- Intraocular pressure increased
- Carbohydrate tolerance decreased
- Increased insulin requirement (or oral hypoglycemic agents in diabetics);
- Nitrogen balance negative (due to protein catabolism);

### Injury, poisoning and procedural complications
- Long bone and spinal compression fracture
- Tendon rupture (particularly of the Achilles tendon)

## INTERACTIONS

The pharmacokinetic interactions listed below are clinically important for all systemic corticosteroids.

Medicines that are cytochrome P450 enzyme (CYP) substrates are metabolised mainly by the CYP3A4 enzyme. CYP3A4 catalyzes, the first metabolic step for corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other medicines) have been shown to alter corticosteroid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

### CYP3A4 INHIBITORS

Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance, resulting in increased plasma concentrations of corticosteroids. These include:

- Antifungals such as ketoconazole and itraconazole
- Antiemetics, such as aprepitant and fosaprepitant
- Immunosuppressants such as cyclosporine
- Macrolide antibacterials such as clarithromycin, erythromycin and troleanomycin
- HIV-Protease inhibitors
- Ciclosporin
- Ritonavir
- Diltiazem
- Grapefruit juice.

Coadministration of these substances may require titration of corticosteroid dosage to reduce the risk of adverse effects and avoid steroid toxicity.

**CYP3A4 INDUCERS**

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentrations of corticosteroids. These include:
- Phenobarbital
- Phenytoin
- Rifampicin
- Rifabutin
- Carbamazepine
- Primidone
- Aminoglutethimide.

Coadministration of these substances may require an increase in corticosteroid dosage to achieve the desired result.

**CYP3A4 SUBSTRATES**

In the presence of another CYP3A4 substrate, the hepatic clearance of corticosteroids may be inhibited or induced, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.

**OTHER INTERACTIONS**

Other interactions and effects that occur with corticosteroids are described below.

**Antacids**

Concurrent use may decrease absorption of corticosteroids. Efficacy may be reduced sufficiently to require dosage adjustments in patients receiving small doses of corticosteroids.

**Antidiabetic agents**

Corticosteroids may increase blood glucose levels. Dose adjustments of antidiabetic therapy may be required with concurrent therapy.
Oral anticoagulants
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 (such as INR or prothrombin time) should be monitored to maintain the desired anticoagulant effects.

Anticholinergics
Corticosteroids may influence the effect of anticholinergics.

Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs.

Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

Cardiac glycosides
There is a risk of toxicity if hypokalaemia occurs due to corticosteroid treatment.

Oral contraceptives
Oral contraceptives retard the metabolism of corticosteroids due to increased binding to globulin, resulting in increased plasma levels of corticosteroids and potentiating their biological effect. The dose of corticosteroids may need to be adjusted when commencing or stopping oral contraceptive therapy.

Diuretics
Excessive potassium loss maybe experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide).

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

NSAIDs
Concomitant administration may increase the risk of gastrointestinal bleeding and ulceration.

Corticosteroids may increase the renal clearance of aspirin. This resulting decrease in salicylate serum levels could lead to an increased risk of salicylate toxicity when the corticosteroid is withdrawn.

Somatropin
Concomitant administration may inhibit the growth promoting effect of somatropin.
**Sympathomimetics**

There is an increased risk of hypokalaemia with concurrent high doses of corticosteroids and sympathomimetics such as salbutamol, salmeterol, terbutaline or formoterol.

**Antivirals**

Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.

Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.

**Antifungals**

The risk of hypokalaemia may be increased with amphotericin.

**Vaccines**

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

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**OVERDOSAGE**

Reports of acute toxicity and metabolic disturbances with corticosteroids are rare but do occur. There is no clinical syndrome of acute overdosage with SOLU CORTEF (hydrocortisone sodium succinate). Hydrocortisone is dialysable. Acute overdose may possibly aggravate pre-existing disease states such as ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema.

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state. The possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time.

In the event of acute overdose, treatment is symptomatic and supportive, including respiratory and cardiovascular function. In chronic toxicity, fluids and electrolytes should be monitored closely. Serum levels are not clinically useful.

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**PHARMACEUTICAL PRECAUTIONS**

**Preparation of Solutions**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Directions for Using the Act-O-Vial System**

1. Tap to ensure that powder is at base of vial and away from the central stopper.
2. Place the Act-O-Vial on a flat, stable surface and hold with one hand.

3. Press down firmly on plastic activator with the palm of the other hand to force diluent into the lower compartment.

4. Gently mix the solution by turning the vial upside down a number of times. DO NOT SHAKE THE VIAL.

5. Remove plastic tab covering centre of stopper.

6. Sterilize top of stopper with a suitable alcohol swab.

7. Whilst vial is on a flat surface, insert needle squarely through centre of stopper until tip is just visible. Invert vial to allow the solution to flow into the top compartment and withdraw dose.

Further dilution is not necessary for intravenous or intramuscular injection. For intravenous infusion, first prepare solution as just described. The 100 mg solution may then be added to 100 to 1000 mL of 5% dextrose in Water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg (hydrocortisone equivalent of hydrocortisone sodium succinate) may be added to 50 mL of the above diluents. The resulting solutions are stable for at least 4 hours and may be administered either directly or by IV "piggy-back".

**Storage Conditions**
Store at or below 25°C. Protect from light.

Use reconstituted solution within 72 hours after mixing.

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**MEDICINE CLASSIFICATION**

Prescription Medicine.

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**PACKAGE QUANTITIES**

SOLU CORTEF 100 mg Act-O-Vial is available as a pack of 1 vial.

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**FURTHER INFORMATION**

Non-proprietary name: hydrocortisone sodium succinate.

The structural formula of hydrocortisone sodium succinate is shown below.
The CAS Registry Number is 125-04-2. The molecular weight is 484.52.

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**NAME AND ADDRESS**

Pfizer New Zealand Ltd  
P O Box 3998  
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

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**DATE OF PREPARATION**

10 November 2014.