

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SOLU-CORTEF[®] hydrocortisone sodium succinate 100 mg Act-O-Vial Powder for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Act-O-Vial is equivalent to 100 mg hydrocortisone sodium succinate when mixed with 2 mL of sterile Water for Injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SOLU-CORTEF is a white or nearly white odourless, hygroscopic amorphous solid, available in Act-O-Vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

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.

4.2 Dose and method of administration

Dose

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 section 4.4).

Method of administration

For instructions on dilution of the medicine before administration, see section <6.6>.

4.3 Contraindications

Hydrocortisone sodium succinate is contraindicated:

- in patients who have systemic fungal infections.
- in patients with known hypersensitivity to the drug or any component of the formulation.
- for use by the intrathecal route of administration,
- for use by the epidural route of administration

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.

4.4 Special warnings and precautions for use

Immunosuppressant 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 and may mask some signs of infection, and new infections may appear during their use. 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.

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. 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.

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 hydrocortisone sodium succinate 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.

Controlled clinical trials have failed to establish the efficacy of SOLU-MEDROL[®] (methylprednisolone sodium succinate) in the treatment of sepsis syndrome and septic shock. Two studies suggest that treatment of these conditions with SOLU-MEDROL may increase the risk of mortality in certain patients (i.e. patients with elevated serum creatinine levels or patients who develop secondary infections after receiving SOLU-MEDROL). Although this trial used SOLU-MEDROL only, Pfizer recommends that SOLU-CORTEF not be used for septic shock or sepsis syndrome either.

Immune System Effects

Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/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.

Endocrine Effects

In patients on corticosteroid therapy (or those who have discontinued treatment but continue to experience symptoms of adrenal insufficiency) subjected to unusual stress such as intercurrent illness, trauma or surgery, increased dosage (or reinstatement) of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

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.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if corticosteroids are withdrawn abruptly.

Drug-induced secondary adrenocortical insufficiency may therefore be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of corticosteroid therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

A steroid “withdrawal syndrome”, seemingly unrelated to adrenocortical insufficiency, may occur following abrupt discontinuance of corticosteroids. 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. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see section 4.8, **General disorders and administration site conditions**).

High doses of corticosteroids can produce or aggravate Cushing’s syndrome, Careful consideration and/or consultation with an endocrinologist are recommended when administering hydrocortisone to patients with Cushing’s disease.

There is an enhanced effect of corticosteroids in patients with hypothyroidism.

Metabolism and Nutrition

Corticosteroids, including hydrocortisone, can increase blood glucose, worsen pre-existing diabetes, and predispose 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.

Psychiatric Effects

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.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. 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. Psychological effects have 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 Effects

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

Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity (also see myopathy statement in section 4.4: ***Musculoskeletal Effects***).

Severe medical events have been reported in association with the intrathecal/epidural routes of administration.

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

Ocular Effects

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, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections 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.

Visual Disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Cardiac Effects

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

Systemic corticosteroids should be 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.

Steroids should be used with caution in patients with hypertension.

Gastrointestinal Effects

High doses of corticosteroids may produce acute pancreatitis.

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. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with nonsteroidal anti-inflammatory drugs (NSAIDs), the risk of developing gastrointestinal ulcers is increased.

Corticosteroids should be used with caution in nonspecific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, oesophagitis and gastritis.

Hepatobiliary Effects

Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring is required. Corticosteroids should be used with caution in patients with hepatic failure.

There is an enhanced effect of corticosteroids in 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

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 generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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 osteoporosis. Corticosteroid 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 Disorders

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.

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.

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.

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.

Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such a regimen should be restricted to the most serious indications. Alternate-day glucocorticoid therapy usually avoids or minimises this side effect. If prolonged therapy is necessary, growth and development of these patients should be carefully monitored.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure. Increased intra-cranial pressure with papilloedema in children

(pseudotumour cerebri) has been reported, usually after treatment withdrawal of other corticosteroids, such as methylprednisolone.

High doses of corticosteroids may produce pancreatitis in children. 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 "Gasping Syndrome" in premature infants. This product DOES NOT contain benzyl alcohol.

Other

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 as to whether daily or intermittent therapy should be used.

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.

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5).

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.

4.5 Interaction with other medicines and other forms of interaction

Hydrocortisone is metabolised by 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) and the cytochrome P450 (CYP) 3A4 enzyme. The CYP3A4 enzyme catalyzes 6 β -hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS - May decrease hepatic clearance and increase the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, and grapefruit juice), the dose of hydrocortisone may need to be decreased to avoid steroid toxicity.

CYP3A4 INDUCERS - May increase hepatic clearance and decrease the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inducer (e.g., rifampin, carbamazepine, phenobarbital, and phenytoin), the dose of hydrocortisone may need to be increased to achieve the desired response.

CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of hydrocortisone may be affected, 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.

NON-CYP3A4-MEDIATED EFFECTS - Other interactions and effects that occur with hydrocortisone are described in Table 1 below.

Table 1 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with hydrocortisone.

Table 1. Important drug or substance interactions/effects with hydrocortisone

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	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 effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see section 4.4, Musculoskeletal Effects , for additional information). 2) 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.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
- FOSAPREPITANT	
Antifungals - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase Inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Cardiac Glycosides - DIGOXIN	Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE)
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
- ERYTHROMYCIN	
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Corticosteroids may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of corticosteroid treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium Depleting Agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

The pharmacokinetic interactions listed below are potentially clinically important.

1. Oral contraceptives retard the metabolism of hydrocortisone due to its increased binding to globulin (transcortin). This increases the plasma levels of hydrocortisone thus potentiating its biological effect.
2. Drugs that induce hepatic enzymes such as phenobarbitone, phenytoin and rifampicin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response.
3. 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.

4.6 Fertility, pregnancy and lactation

Fertility

Corticosteroids have been shown to impair fertility in animal studies.

Pregnancy

Pregnancy Category C

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 foetal malformations (cleft palate, skeletal malformations) and abortion. These findings do not seem to be relevant to human beings. Some corticosteroids readily cross the placenta. Reduced placental and birth weight have also been recorded in animals and human after long-term maternal treatment along with potential for suppression of the adrenal cortex in newborns. 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 foetus when prescribing corticosteroids. Some retrospective studies have found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimised by administering lower corticosteroid doses. The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the foetus or the newborn infant.

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency.

Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Breast-feeding

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

4.7 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.

4.8 Undesirable 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.

<i>Infections and Infestations</i>	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)
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
<i>Blood and lymphatic system disorders</i>	Leucocytosis
<i>Immune system disorders</i>	Drug hypersensitivity (including anaphylaxis and anaphylactoid reactions [e.g., bronchospasm, laryngeal oedema, urticaria])
<i>Endocrine disorders</i>	Cushingoid Hypopituitarism Manifestation of latent diabetes Steroid withdrawal syndrome
<i>Intraocular pressure increased Carbohydrate tolerance decreased</i>	Metabolic acidosis Alkalosis hypokalaemic Dyslipidaemia Fluid retention Increased insulin requirement (or oral hypoglycemic agents in diabetics) Lipomatosis Increased appetite (which may result in weight gain) Sodium retention Glucose tolerance impaired
<i>Psychiatric disorders</i>	Affective disorder (including euphoric mood, affect lability, drug dependence, suicidal ideation, depression) Psychotic disorder (including mania, delusion, hallucination and schizophrenia) Behavioural disturbances (including irritability, anxiety, insomnia, mood swing, personality change) Cognitive dysfunction including confusional state Abnormal behaviour Mental disorder
<i>Nervous system disorders</i>	Seizure Dizziness Headache Intracranial pressure increased (with papilloedema) Benign intracranial hypertension Epidural lipomatosis Amnesia Cognitive disorder

<i>Eye disorders</i>	Central serous retinopathy Cataract Glaucoma Exophthalmos Central serous chorioretinopathy Corneal thinning Scleral thinning Exacerbation of ophthalmic viral or fungal disease Vision, blurred (see also section 4.4)
<i>Ear and labyrinth disorders</i>	Vertigo
<i>Cardiac disorders</i>	Cardiac failure congestive (in susceptible patients)
<i>Vascular disorders</i>	Thrombosis Hypertension Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>	Pulmonary embolism Gasping Syndrome Hiccups
<i>Gastrointestinal disorders</i>	Abdominal distension Abdominal pain Diarrhoea Dyspepsia Nausea Oesophagitis Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage) Pancreatitis Gastric haemorrhage Intestinal perforation
<i>Skin and subcutaneous tissue disorders</i>	Angioedema Ecchymosis Hirsutism Hyperhidrosis Petechiae Pruritus Rash Skin atrophy Erythema Skin striae Urticaria Acne Telangiectasia Hyperpigmentation or hypopigmentation Sterile abscess

<i>Musculoskeletal and connective tissue disorders</i>	Muscular weakness Myalgia Myopathy Muscle atrophy Osteonecrosis Osteoporosis Pathologic fractures Neuropathic arthropathy Arthralgia Growth retardation
<i>Reproductive system and breast disorders</i>	Menstruation irregular Amenorrhoea
<i>General disorders and administration site conditions</i>	Fatigue Impaired healing Oedema peripheral Malaise Injection site reaction
<i>Investigations</i>	Alanine aminotransferase increased Aspartate aminotransferase increased Blood alkaline phosphatase increased Blood potassium decreased Urine calcium increased Intraocular pressure increased Carbohydrate tolerance decreased Blood urea increased Suppression of reactions to skin tests Nitrogen balance negative (due to protein catabolism);
<i>Injury, poisoning and procedural complications</i>	Long bone and spinal compression fracture Tendon rupture (particularly of the Achilles tendon)

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms and Signs

Reports of acute toxicity and metabolic disturbances with corticosteroids are rare but do occur. There is no clinical syndrome of acute overdosage with 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.

Treatment

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

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

5.3 Preclinical safety data

Unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic sodium phosphate,
Monobasic sodium phosphate monohydrate,
Sodium hydroxide.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

60 months from date of manufacture stored at or below 25°.
3 days reconstituted stored at or below 25°C.

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

*To avoid microbial contamination hazards, the further diluted solutions should be used as soon as practicable. If storage is necessary, hold reconstituted/diluted solutions at 2°- 8°C for not more than 24 hours. Any solution not used within 24 hours should be discarded. **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

4. Tap to ensure that powder is at base of vial and away from the central stopper.
5. Place the Act-O-Vial on a flat, stable surface and hold with one hand.
6. Press down firmly on plastic activator with the palm of the other hand to force diluent into the lower compartment.
7. Gently mix the solution by turning the vial upside down a number of times. **DO NOT SHAKE THE VIAL.**

8. Remove plastic tab covering centre of stopper.
9. Sterilise top of stopper with a suitable alcohol swab.

Note: Steps 1-6 must be completed before proceeding.

10. 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".

7. Medicine SCHEDULE

Prescription Medicine.

8. SPONSOR

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

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

14 July 1972.

10. DATE OF REVISION OF THE TEXT

13 June 2019.

Summary of Updates

Section	Update

Section 4.1	<p>Removal of the following indication in line with the company held core datasheet:</p> <p><i>Nervous System</i> Acute exacerbations of multiple sclerosis.</p>
Section 4.4	<p>Removal of the following text as is it associated with the indication being removed:</p> <p>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 section 4.2).</p>
Section 6.1	<p>Excipients are amended to align with Australian AAN as per Australian Product Information.</p>