HYDROCORTISONE SODIUM SUCCINATE

℞

SOLU-CORTEF®

100 mg, 100 mg/2 mL, 250 mg/2 mL, 500 mg/4 mL Sterile Powder for Injection (IM/IV)

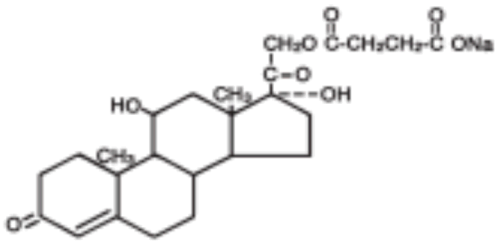
1.0 PHARMACOLOGIC CATEGORY

Corticosteroid.

2.0 DESCRIPTION

Solu-Cortef® (hydrocortisone sodium succinate or pregn-4-ene-3, 20-dione, 21-(3-carboxy-1-oxopropoxy)-11, 17-dihydroxy); monosodium salt, (11β) 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.

The structural formula is represented below:



When necessary the pH of hydrocortisone sodium succinate (Solu-Cortef®) was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8.

3.0 FORMULATION/COMPOSITION

Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone, 1 mg monobasic sodium phosphate, 9 mg dibasic sodium, and 10% sodium hydroxide.

Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg/2 mL Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone/2 mL, 1 mg monobasic sodium phosphate, 10 mg dibasic sodium, and 10% sodium hydroxide.

Hydrocortisone sodium succinate (Solu-Cortef®) 250 mg/2 mL Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 250 mg hydrocortisone/2 mL, 2 mg monobasic sodium phosphate, 25 mg dibasic sodium phosphate, and 10% sodium hydroxide.

Hydrocortisone sodium succinate (Solu-Cortef®) 500 mg/4 mL Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 500 mg

hydrocortisone/4 mL, 5 mg monobasic sodium phosphate, 52 mg dibasic sodium phosphate, and 10% sodium hydroxide.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency
Acute adrenocortical insufficiency
Pre-operatively, 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
Non-suppurative thyroiditis
Hypercalcemia associated with cancer

2. Non-endocrine Disorders

Rheumatic Disorders — As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Acute and subacute bursitis
Acute gouty arthritis
Acute non-specific tenosynovitis
Ankylosing spondylitis
Epicondylitis
Post-traumatic osteoarthritis
Psoriatic arthritis
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
Synovitis of osteoarthritis

Collagen Diseases — During an exacerbation or as maintenance therapy in selected cases of:
Acute rheumatic carditis
Systemic dermatomyositis (polymyositis)
Systemic lupus erythematosus

Dermatologic Diseases
Bullous dermatitis herpetiformis
Exfoliative dermatitis
Mycosis fungoides
Pemphigus
Severe erythema multiforme (Stevens-Johnson syndrome)
Severe psoriasis
Severe seborrheic dermatitis

Allergic States – Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
Acute non-infectious laryngeal edema
Atopic dermatitis
Bronchial asthma
Contact dermatitis
Drug hypersensitivity reactions
Serum sickness
Urticarial transfusion reactions

Ophthalmic Diseases – Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
Allergic conjunctivitis
Allergic corneal marginal ulcers
Anterior segment inflammation
Chorioretinitis
Diffuse posterior uveitis and choroiditis
Herpes zoster ophthalmicus
Iritis and iridocyclitis
Keratitis
Optic neuritis
Sympathetic ophthalmia

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

Respiratory Diseases
Aspiration pneumonitis
Berylliosis
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
Loeffler's syndrome not manageable by other means
Symptomatic sarcoidosis

Hematologic Disorders
Acquired (autoimmune) hemolytic anemia
Congenital (erythroid) hypoplastic anemia
Erythroblastopenia (RBC anemia)
Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)
Secondary thrombocytopenia in adults

Neoplastic Diseases – For palliative management of:
Acute leukemia of childhood
Leukemias and lymphomas in adults

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

Medical Emergencies
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 hemorrhagic, traumatic and surgical shock in which standard therapy (e.g., fluid replacement) has not been effective (see **Section 4.4 Special Warnings and Precautions for Use**).

Miscellaneous
Trichinosis with neurologic or myocardial involvement.

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

4.2 Dosage and Method of Administration

This preparation may be administered by intravenous injection or infusion or by intramuscular injection. The preferred method for initial emergency use is 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 the drug 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).

Dosage requirements are variable and must be individualized on the basis of the disease under treatment, its severity and the response of the patient over the entire duration of treatment. A risk/benefit decision must be made in each individual case on an ongoing basis.

The lowest possible dose of corticosteroid should be used to control the condition under treatment for the minimum period. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached.

In general, high-dose corticosteroid therapy should be continued only until the patient’s condition has stabilized -- 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 to 72 hours, hypernatremia may occur. Under such circumstances it may be desirable to replace hydrocortisone sodium succinate with a corticoid product such as one containing methylprednisolone sodium succinate which causes little or no sodium retention.

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see **Section 4.4 Special Warnings and Precautions for Use**).

The initial dose 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.

In patients with liver disease, there may be an increased effect (see **Section 4.4 Special Warnings and Precautions for Use**) and reduced dosing may be considered.

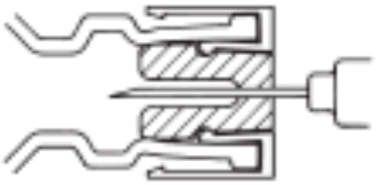
Preparation of Solutions
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

100 mg Plain or with Bacteriostatic Water for Injection -- For intravenous or intramuscular injection, prepare solution by aseptically adding not more than 2 mL of Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride Injection to the contents of one vial. For intravenous infusion, first prepare solution by adding not more than 2 mL of Bacteriostatic Water for Injection to the vial: This solution may then be added to 100 to 1000 mL of the following: 5% dextrose in Water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

Directions for using Act-O-Vial Two-Compartment Vial
1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.

Note: Steps 1-4 must be completed before proceeding.

5. Insert needle squarely through center of plunger-stopper until tip is just visible (as illustrated).
6. Invert vial 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). The 250 mg solution may be added to 250 to 1000 mL, the 500 mg solution may be added to 500 to 1000 mL, and the 1000 mg solution to 1000 mL of the same diluents. 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."

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, such as Hydrocortisone sodium succinate, Monobasic sodium phosphate anhydrous, Dibasic sodium phosphate dried, 10% Sodium hydroxide.
- for use by the intrathecal route of administration, except as part of certain chemotherapeutic regimens (diluents containing benzyl alcohol must not be used).
- for use by the epidural route of administration.

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

4.4 Special Warnings and Precautions for Use

Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, 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.

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

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

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 subjected to unusual stress, increased dosage 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 glucocorticoid therapy.

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

Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for

months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

There is an enhanced effect of corticosteroids on 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.

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.

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 (also see myopathy statement in **Section 4.4 Special Warnings and Precautions for Use, 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 for fear of 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 glucocorticoids.

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

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 cases of 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, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage 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 non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections, also in diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary Effects
Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore, appropriate monitoring is required.

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 described 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 quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Osteoporosis is generally associated with long-term use and large doses of glucocorticoids. Corticosteroids should be used with caution in patients with osteoporosis.

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 therefore, should not be used to treat, traumatic brain injury; a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

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 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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.

In post marketing experience tumor lysis syndrome (TLS) has been reported in patients with malignancies, including hematological malignancies and solid tumors, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumors that have a high proliferative rate, high tumor burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

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

Growth may be suppressed in children receiving long-term, daily-divided dose glucocorticoid therapy. The use of such a regimen should be restricted to the most serious indications.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Hydrocortisone is metabolized by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and the cytochrome P450 (CYP) 3A4 enzyme. The CYP3A4 enzyme catalyzes 6β-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 co-administration.

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 Special Warnings and Precautions for Use, 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 - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
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	CYP3A4 INHIBITOR (and SUBSTRATE)

Drug Class or Type **- DRUG or SUBSTANCE**	**Interaction/Effect**
- DILTIAZEM	
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.
Estrogens (including oral contraceptives containing estrogens)	CYP3A4 INHIBITOR (and SUBSTRATE) Estrogens may potentiate effects of hydrocortisone by increasing the concentration of transcortin and thus decreasing the amount of hydrocortisone available to be metabolized. Dosage adjustments of hydrocortisone may be required if estrogens are added to or withdrawn from a stable dosage regimen.
- 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 - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
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.

4.6 Fertility, Pregnancy and Lactation

Fertility

Corticosteroids have been shown to impair fertility in animal studies (see **Section 5.3 Preclinical Safety Data**).

Pregnancy

Some animal studies have shown that corticosteroids, including hydrocortisone, when administered to the mother at high doses, may cause fetal malformations. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women. Since adequate human reproductive studies have not been done with hydrocortisone sodium succinate, this medicinal product should be used during

pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Some corticosteroids readily cross the placenta. 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 minimized by administering lower corticosteroid doses. 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 labor and delivery.

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

Lactation
Corticosteroids are excreted in breast milk.

This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

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

NOTE: The following are typical for all systemic corticosteroids. Their inclusion in this list does not necessarily indicate that the specific event has been observed with this particular formulation.

Adverse Reactions Table	
System Organ Class	**Adverse Drug Reactions**
Infections and infestations	Opportunistic infection; Infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction
Endocrine disorders	Cushingoid; Hypothalamic pituitary adrenal axis suppression; Steroid withdrawal syndrome
Metabolism and nutrition disorders	Metabolic acidosis; Sodium retention; Fluid retention; Alkalosis hypokalemic; Dyslipidemia; Glucose tolerance impaired; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Lipomatosis; Increased appetite (which may result in Weight increased)
Psychiatric disorders	Affective disorder (including Depression, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation); Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia);

Adverse Reactions Table	
System Organ Class	**Adverse Drug Reactions**
	Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behavior; Insomnia; Irritability
Nervous system disorders	Epidural lipomatosis; Intracranial pressure increased; Benign intracranial hypertension; Seizure; Amnesia; Cognitive disorder; Dizziness; Headache
Eye disorders	Central serous chorioretinopathy; Cataract; Glaucoma; Exophthalmos
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Cardiac failure congestive (in susceptible patients); Hypertrophic cardiomyopathy (in prematurely born infants)
Vascular disorders	Thrombosis; Hypertension; Hypotension
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism; Gasping Syndrome; Hiccups
Gastrointestinal disorders	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer hemorrhage); Intestinal perforation; Gastric hemorrhage; Pancreatitis; Esophagitis; Abdominal distension; Abdominal pain; Diarrhea; Dyspepsia; Nausea
Skin and subcutaneous tissue disorders	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation
Musculoskeletal and connective tissue disorders	Muscular weakness; Myalgia; Myopathy; Muscle atrophy; Osteoporosis; Osteonecrosis; Pathological fracture; Neuropathic arthropathy; Arthralgia; Growth retardation
Reproductive system and breast disorders	Menstruation irregular
General disorders and administration site conditions	Impaired healing; Edema peripheral; Fatigue; Malaise; Injection site reaction
Investigations	Intraocular pressure increased; Carbohydrate tolerance decreased; Blood potassium decreased; Urine calcium increased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Blood urea increased; Suppression of reactions to skin tests*
Injury, poisoning and procedural complications	Spinal compression fracture; Tendon rupture

* Not a MedDRA PT

4.9 Overdose and Treatment

There is no clinical syndrome of acute overdosage with corticosteroids. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

Hydrocortisone is dialyzable.

5.0 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The 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. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is five to one. This is consistent with the relative oral potency of methylprednisolone and hydrocortisone.

5.2 Pharmacokinetic Properties

The pharmacokinetics of hydrocortisone in healthy male subjects demonstrated nonlinear kinetics when a single intravenous dose of hydrocortisone sodium succinate higher than 20 mg was administered, and the corresponding pharmacokinetic parameters of hydrocortisone are presented in Table 2.

Table 2. Mean (SD) hydrocortisone pharmacokinetic parameters following single intravenous doses

	Healthy Male Adults (21-29 years; N = 6)			
Dose (mg)	5	10	20	40
Total Exposure ($AUC_{0-\infty}$; ng·h/mL)	410 (80)	790 (100)	1480 (310)	2290 (260)
Clearance (CL; mL/min/m^2)	209 (42)	218 (23)	239 (44)	294 (34)
Volume of Distribution at Steady State (V_{dss}; L)	20.7 (7.3)	20.8 (4.3)	26.0 (4.1)	37.5 (5.8)
Elimination Half-life ($t_{1/2}$; hr)	1.3 (0.3)	1.3 (0.2)	1.7 (0.2)	1.9 (0.1)

$AUC_{0-\infty}$ = Area under the curve from time zero to infinity.

Absorption

Following administration of 5, 10, 20, and 40 mg single intravenous doses of hydrocortisone sodium succinate in healthy male subjects, mean peak values obtained at 10 minutes after dosing were 312, 573, 1095, and 1854 ng/mL, respectively. Hydrocortisone sodium succinate is rapidly absorbed when administered intramuscularly.

Distribution
Hydrocortisone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The volume of distribution at steady state for hydrocortisone ranged from approximately 20 to 40 L (Table 2). Hydrocortisone binds to the glycoprotein transcortin (i.e., corticosteroid binding globulin) and albumin. The plasma protein binding of hydrocortisone in humans is approximately 92%.

Metabolism
Hydrocortisone (i.e., cortisol) is metabolized by 11β-HSD2 to cortisone, and further to dihydrocortisone and tetrahydrocortisone. Other metabolites include dihydrocortisol, 5α-dihydrocortisol, tetrahydrocortisol, and 5α-tetrahydrocortisol. Cortisone can be converted to cortisol through 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).

Hydrocortisone is also metabolized by CYP3A4 to 6β-hydroxycortisol (6β-OHF), and 6β-OHF varied from 2.8% to 31.7% of the total metabolites produced, demonstrating large inter-individual variability.

Excretion
Excretion of the administered dose is nearly complete within 12 hours. When hydrocortisone sodium succinate is administered intramuscularly, it is excreted in a pattern similar to that observed after intravenous injection.

5.3 Preclinical Safety Data

Carcinogenesis
Hydrocortisone did not increase tumor incidences in male and female rats during a 2-year carcinogenicity study.

Mutagenesis
Corticosteroids, a class of steroid hormones that includes hydrocortisone, are consistently negative in the bacterial mutagenicity assay. Hydrocortisone and dexamethasone induced chromosome aberrations in human lymphocytes *in vitro* and in mice *in vivo*. However, the biological relevance of these findings is not clear since hydrocortisone did not increase tumor incidences in male and female rats during a 2-year carcinogenicity study. Fludrocortisone (9α-fluorohydrocortisone, structurally similar to hydrocortisone) was negative in the human lymphocyte chromosome aberration assay.

Reproductive toxicity
Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids

have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth retardation. With hydrocortisone, cleft palate was observed when administered to pregnant mice and hamsters during organogenesis.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date of the product.

6.2 Storage Conditions

Store unreconstituted product at controlled temperature 15°C to 30°C.

Store solution at controlled temperature 15°C to 30°C and protect from light. Use solution only if it is clear. Unused solution should be discarded after 3 days.

6.3 Availability

Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg Sterile Powder for Injection (IM/IV) vial x 1's
Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg/2 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's
Hydrocortisone sodium succinate (Solu-Cortef®) 250 mg/2 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's
Hydrocortisone sodium succinate (Solu-Cortef®) 500 mg/4 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's

6.4 Special Precautions for Disposal and Other Handling

Protect from light. Use solution only if it is clear.
Unused solution should be discarded after 3 days.

7.0 FDA REGISTRATION NUMBER

Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg Sterile Powder for Injection (IM/IV) vial x 1's – DRP-2145
Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg/2 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's - DRP-2154
Hydrocortisone sodium succinate (Solu-Cortef®) 250 mg/2 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's - DRP-2129
Hydrocortisone sodium succinate (Solu-Cortef®) 500 mg/4 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1' - DRP-2127

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg Sterile Powder for Injection (IM/IV) vial x 1's – 14 Dec 1990

Hydrocortisone sodium succinate (Solu-Cortef®) 100 mg/2 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's-05 June 1987
Hydrocortisone sodium succinate (Solu-Cortef®) 250 mg/2 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's- 20 Sept 1967
Hydrocortisone sodium succinate (Solu-Cortef®) 500 mg/4 mL Sterile Powder for Injection (IM/IV) ACT-O-VIAL x 1's- 26 Aug 1971

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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