PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSOLU-CORTEF*

Hydrocortisone sodium succinate for injection USP

Sterile Powder and Diluent

100 mg, 250 mg, 500 mg and 1 g Act-O-Vials†

Glucocorticoid

Pfizer Canada ULC
17,300 Trans-Canada Highway
Kirkland, Québec H9J 2M5

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.1 Dosing considerations	09/2021

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Sections or subsections that are not applicable at the time of authorization are not listed .

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SOLU-CORTEF (Hydrocortisone sodium succinate for injection USP) is indicated for:

1. **Endocrine Disorders**

   - In primary, secondary and acute 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).
   - Congenital adrenal hyperplasia
   - Nonsuppurative thyroiditis
   - Hypercalcemia associated with cancer

2. **Rheumatic Disorders**

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

3. **Collagen Diseases**

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

4. **Dermatologic Diseases**

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

5. **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
- Drug hypersensitivity reactions
- Urticarial transfusion reactions

6. **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

7. **Gastrointestinal Diseases**

To tide the patient over a critical period of the disease in:

- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy)

8. **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

9. **Hematologic Disorders**

- Acquired (autoimmune) hemolytic anemia
- Idiopathic thrombocytopenia purpura in adults (intravenous [I.V.] only; intramuscular [I.M.] administration is contraindicated)
- Erythroblastopenia (RBC anemia)

- Congenital (erythroid) hypoplastic anemia
- Secondary thrombocytopenia in adults

10. **Neoplastic Diseases**

    For palliative management of:
    - Leukemias and lymphomas in adults
    - Acute leukemia of childhood

11. **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.

12. **Medical Emergencies**

    - in the treatment of shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present
    - preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
    - in the treatment of acute allergic disorders (status asthmaticus, anaphylactic reactions, insect stings, noninfectious laryngeal edema, etc.) following epinephrine (see **7 WARNINGS AND PRECAUTIONS**).

13. **Miscellaneous**

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

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of [SOLU-CORTEF] in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see **7 WARNINGS AND PRECAUTIONS**, **7.1.3 Pediatrics**, **4 DOSAGE AND ADMINISTRATION**).

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see **7 WARNINGS AND PRECAUTIONS**, **7.1.4 Geriatrics**, **4 DOSAGE AND ADMINISTRATION**).

2 CONTRAINDICATIONS

SOLU-CORTEF (hydrocortisone sodium succinate) is contraindicated:

- in patients with known hypersensitivity to any components of the product (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**);

- in patients with systemic fungal infections;
- in idiopathic thrombocytopenic purpura when administered intramuscularly;
- in patients administered with live or live, attenuated vaccines while receiving immunosuppressive doses of corticosteroids;
- in herpes simplex of the eye, except when used for short-term or emergency therapy as in acute sensitivity reactions;
- in patients with vaccinia and varicella, except when used for short-term or emergency therapy as in acute sensitivity reactions.

SOLU-CORTEF is not indicated for epidural route of administration.

SOLU-CORTEF is not indicated for intrathecal route of administration, except as part of certain chemotherapeutic regimens (diluents containing benzyl alcohol must not be used).

Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

Dosage adjustments may be necessary if there are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition.

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.

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see **7 WARNINGS AND PRECAUTIONS**).

4.2 Recommended Dose and Dosage Adjustment

The initial dose of SOLU-CORTEF is 100 mg to 500 mg or more depending on the severity of the condition. Therapy is initiated by administering SOLU-CORTEF intravenously over a period of 30 seconds (e.g., 100 mg) to 10 minutes (e.g., 500 mg or more). This dose may be repeated at intervals of 2, 4, or 6

hours as indicated by the patient's response and clinical condition. If constantly high blood levels are required, SOLU-CORTEF should be injected every 4 to 6 hours. In general, high-dose corticosteroid therapy should be continued only until the patient's condition has stabilized, usually not beyond 48 to 72 hours. 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 corticosteroid product such as methylprednisolone sodium succinate that causes little or no sodium retention.

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

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 **7 WARNINGS AND PRECAUTIONS**) and reduced dosing may be considered.

Special Populations

Pediatrics
Dosing in infants and children is governed more by the severity of the condition and response of the patient than by age or body weight. The daily dose should be not less than 25 mg.

Geriatrics
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.3 Reconstitution

Parenteral Products:

Intravenous/Intramuscular Injection
For intravenous/intramuscular injection, reconstitute Act-O-Vials according to instructions. Further dilution is not necessary for intravenous or intramuscular injection.

Intramuscular injections of corticosteroids should be given deep into large muscle masses to avoid local tissue atrophy.

Intravenous Infusion
For intravenous infusion, first reconstitute Act-O-Vials according to instructions. The solution can then be combined with a diluent. The following diluents may be used:
5% Dextrose in water or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction.

The **100 mg** solution may be added to 100 to 1000 mL of diluent.
The **250 mg** solution may be added to 250 to 1000 mL of diluent.
The **500 mg** solution may be added to 500 to 1000 mL of diluent.
The **1000 mg** solution may be added to 1000 mL of diluent.

In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg of SOLU-CORTEF may be added to 50 mL of the above diluents. The resulting solutions may be administered either directly or by I.V. piggyback.

The following table provides the stability data of hydrocortisone in 5% Dextrose in Water USP or 0.9% Sodium Chloride Injection, USP, at room temperature.

SOLU-CORTEF Stability	
CONCENTRATION	**STABILITY (Time)**
0.5 mg/mL - 20 mg/mL	4 hours

Therefore, after the reconstituted solution has been diluted for intravenous infusion, unused solution should be discarded after 4 hours.

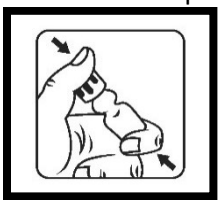
The Act-O-Vial is a single dose vial and once reconstituted solution is used, any remaining portion should be discarded.

4.4 Administration

SOLU-CORTEF comes in a two-compartment vial (Act-O-Vial) containing sterile white powder in the lower compartment and sterile water in the upper compartment. To use SOLU-CORTEF Act-O-Vial reconstitute Act-O-Vial according to DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

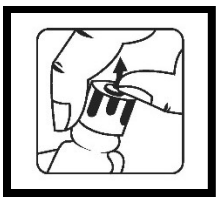
DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

1. Press down on plastic activator to force diluent into the lower compartment.

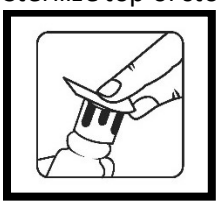


2. Gently agitate to effect solution.

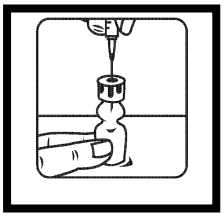
3. Remove plastic tab covering center of stopper.



4. Sterilize top of stopper with a suitable germicide.



5. Insert needle squarely through center of stopper until tip is just visible.



6. Invert vial and withdraw dose.

5 OVERDOSAGE

Hydrocortisone is dialyzable.

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

Continuous overdosage would require careful gradual reduction of dosage in order to prevent the occurrence of acute adrenal insufficiency.

Complications resulting from the metabolic effects of the corticosteroid should be handled as appropriate. Maintain adequate fluid intake and monitor electrolytes in serum and urine, with particular attention to sodium and potassium balance. Treat electrolyte imbalance if necessary.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Intravenous injection Intravenous infusion Intramuscular injection	100 mg, 250 mg, 500 mg and 1 g	Sterile powder: Dibasic sodium phosphate dried, Monobasic sodium phosphate anhydrous Diluent: Sterile water for injection

Each SOLU-CORTEF Act-O-Vial contains:

SOLU-CORTEF	100 mg Act-O-Vial	250 mg Act-O-Vial	500 mg Act-O-Vial	1 g Act-O-Vial
POWDER				
Hydrocortisone (as hydrocortisone sodium succinate)	100 mg	250 mg	500 mg	1000 mg
Monobasic Sodium Phosphate Anhydrous	0.8 mg	2 mg	4 mg	8 mg
Dibasic Sodium Phosphate Dried	8.73 mg	21.8 mg	44 mg	87.32 mg
DILUENT				
Sterile Water for Injection	2 mL	2 mL	4 mL	8 mL

Availability:

SOLU-CORTEF 100 mg Act-O-Vials are packaged in cartons of 10.

SOLU-CORTEF 250 mg Act-O-Vials are packaged in cartons of 10.

SOLU-CORTEF 500 mg Act-O-Vials are packaged in cartons of 5.

SOLU-CORTEF 1 g Act-O-Vials are packaged in cartons of 5.

7 WARNINGS AND PRECAUTIONS

General

SOLU-CORTEF 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.

Intramuscular injections of corticosteroids should be given deep into large muscle masses to avoid local tissue atrophy.

The lowest possible dose of corticosteroid should be used to control the condition under treatment; when dosage reduction is possible, the reduction should be gradual. Since complications of corticosteroid treatment are dependent on dose size and duration of treatment, a risk/benefit decision must be made with each patient as to whether daily or intermittent therapy should be used.

Advise patients to inform subsequent health professional of the prior use of corticosteroids.

The existence of diabetes, osteoporosis, renal insufficiency, chronic psychosis, hypertension, myasthenia gravis or predisposition to thrombophlebitis requires that SOLU-CORTEF be administered with caution.

Carcinogenesis and Mutagenesis

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

Animal studies found corticosteroids to have possible mutagenic potential (see **16 NON-CLINICAL TOXICOLOGY**, **Mutagenicity**).

Cardiovascular

Average and large doses of hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with synthetic derivatives except when used in large doses. Dietary salt restriction to below 500 mg per day and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, corticosteroids should be used with caution, and only if strictly necessary, in patients with congestive heart failure.

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.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

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.

Driving and Operating Machinery

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

Endocrine and Metabolism

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. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, if stress occurs during that period, therapy with corticosteroids should be reinstituted. If the patient is currently receiving corticosteroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticosteroid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. 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. Drug-induced adrenocortical insufficiency may be minimized by gradual reduction of dosage.

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

Corticosteroids, including hydrocortisone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

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

Gastrointestinal

Corticosteroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, when corticosteroids are used as direct or adjunctive therapy, since they may increase the risk of a perforation.

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), such as Aspirin (acetylsalicylic acid), the risk of developing gastrointestinal ulcers is increased.

Hematologic

Aspirin (acetylsalicylic acid) should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia (see **9 DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

The hepatobiliary disorders are a class effect of corticosteroids including hydrocortisone. Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore, appropriate monitoring of hepatic function 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.
There is an enhanced effect of corticosteroids in patients with cirrhosis.
High doses of corticosteroids may produce acute pancreatitis.

Immune

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.

SOLU-CORTEF should not be used for local effect by intra-articular, intrabursal, or intratendinous administration in the presence of acute local infection.

Fungal Infections
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **2 CONTRAINDICATIONS**; **9 DRUG INTERACTIONS**).

Special pathogens
Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis and Toxoplasma.

It is recommended that amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) 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 septicemia.
Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Viral Infections
Chickenpox and measles can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be

taken to avoid exposure. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled i.m. immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.
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.

Recent studies do not support SOLU-CORTEF use during septic shock and suggest that increased mortality may occur in some subgroups of patients at higher risk (i.e., elevated creatinine greater than 2 mg/dL or with secondary infections).

Vaccination
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see **2 CONTRAINDICATIONS**). 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.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially in high doses, because of possible hazards of neurological complications and lack of antibody response.

Tuberculosis
The use of SOLU-CORTEF 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.

Monitoring and Laboratory Tests

Corticosteroids may suppress reactions to skin tests.

Monitoring for signs and symptoms of drug-induced secondary adrenocortical insufficiency may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.

Musculoskeletal

An acute myopathy has been observed 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 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.

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Corticosteroids should be used with caution in patients with osteoporosis and in patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy. Osteoporosis is an adverse effect generally associated with long-term use and large doses of glucocorticoids.

Neurologic

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

Systemic corticosteroids, including SOLU-CORTEF, are not indicated for, and therefore should not be used for the treatment of traumatic brain injury, as demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo.

Corticosteroids should be used with caution in patients with myasthenia gravis.

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

Ophthalmologic

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, and nuclear cataracts (particularly in children), exophthalmos, or increased ocular pressure, which may result in glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. As intraocular pressure may become elevated in some individuals, if steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex except when used for short-term or emergency therapy as in acute sensitivity reactions.

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

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.

Potentially severe psychiatric adverse reactions may occur with systemic steroids (see **8 ADVERSE REACTIONS**). 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.

Renal

Corticosteroids should be used with caution in patients with renal insufficiency.

Reproductive Health: Female and Male Potential

Fertility

Steroids may increase or decrease motility and number of spermatozoa in some patients (see **16 NON-CLINICAL TOXICOLOGY**).

Sensitivity/Resistance

Allergic reactions (e.g., angioedema) may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug (see **8 ADVERSE REACTIONS**)**.**

Skin

Injection of SOLU-CORTEF may result in dermal and/or subdermal changes forming depressions in the skin at the injection site. In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

7.1 Special Populations

7.1.1 Pregnant Women

Corticosteroids readily cross the placenta.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits, have yielded an increase incidence of cleft palate in the off-spring. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.

There are no adequate and well-controlled studies in pregnant women. Some retrospective studies have found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids. The risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses. Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Since there is inadequate evidence of safety in human pregnancy, SOLU-CORTEF should be used during pregnancy at the lowest possible dose, only if clearly needed and the potential benefit justifies the potential risk to the embryo or fetus.

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.

7.1.2 Breast-feeding

Systemically administered corticosteroids are excreted in breast milk and may suppress infant growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a careful benefit-risk assessment should be conducted and a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age)

Pediatric patients may experience a decrease in their growth velocity at low systemic doses and in the absence of laboratory evidence of HPA axis suppression. Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose over the shortest period of time.

The growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis.

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 as one of the adverse effects of prophylactic or therapeutic administration of hydrocortisone to prematurely born infants and few months old babies (< 12 months), therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure must be performed (preferably two-dimensional echocardiography).

7.1.4 Geriatrics

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following Adverse Reactions have been reported with the systemic use of SOLU-CORTEF and/or other corticosteroid preparations.

Table 1. Adverse Reactions	
System Organ Class	**Adverse Drug Reactions**
Infections and infestations	Opportunistic infection; Infection; Infection susceptibility increased
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; Hypopituitarism; Hirsutism; Hypertrichosis; Abnormal fat deposits; Weight increased; Moon face; Glycosuria; Steroid withdrawal syndrome
Metabolism and nutrition disorders	Metabolic acidosis; Sodium retention; Fluid retention; Alkalosis hypokalaemic; Dyslipidaemia; Glucose tolerance impaired; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Lipomatosis; Increased appetite (which may result in weight increased) Nitrogen balance negative (due to protein catabolism)
Psychiatric disorders	Affective disorder (including depression, euphoric mood, affect lability, drug dependence, suicidal ideation); Psychotic disorder (including mania, delusion, hallucination and schizophrenia); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings;

Table 1. Adverse Reactions	
System Organ Class	**Adverse Drug Reactions**
	Abnormal behavior; Insomnia; Irritability
Nervous system disorders	Intracranial pressure increased with papilloedema (benign intracranial hypertension) usually following discontinuation of treatment; Seizure; Amnesia; Cognitive disorder; Dizziness; Headache; Neuritis; Neuropathy peripheral; Paraesthesia; Arachnoiditis; Meningitis; Paraparesis/paraplegia; Sensory disturbance has occurred after intrathecal administration; Epidural lipomatosis
Eye disorders	Cataract; Exophthalmos; Glaucoma; Rare instances of blindness associated with periocular injections; Central serous chorioretinopathy
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Cardiac failure congestive (in susceptible patients); Bradycardia; Cardiac arrest; Arrhythmia; Cardiomegaly; Circulatory collapse; Fat embolism; Hypertrophic cardiomyopathy in premature infants; Myocardial rupture following recent myocardial infarction (see WARNINGS AND PRECAUTIONS); Pulmonary oedema; Syncope; Tachycardia; Embolism; Thrombophlebitis; Vasculitis
Vascular disorders	Hypertension; Hypotension;

Table 1. Adverse Reactions	
System Organ Class	**Adverse Drug Reactions**
	Thrombosis
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism; Hiccups
Gastrointestinal disorders	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer hemorrhage); Gastric hemorrhage; Pancreatitis; Oesophagitis ulcerative; Intestinal perforation (of the small and large intestine, particularly in patients with inflammatory bowel disease); Abdominal distension; Abdominal pain; Diarrhoea; Dyspepsia; Bowel/bladder dysfunction (after intrathecal administration); Increased appetite (which may result in weight increased); Nausea; Elevation in serum liver enzyme levels (usually reversible upon discontinuation)
Skin and subcutaneous tissue disorders	Angioedema; Petechiae; Ecchymosis; Cutaneous and subcutaneous atrophy; Skin atrophy; Acne; Dermatitis allergic; Burning sensation or tingling (especially in the perineal area, after intravenous injection); Dry skin / Skin exfoliation; Erythema; Skin hyperpigmentation; Skin hypopigmentation; Hyperhidrosis; Rash; Abscess sterile; Skin striae; Alopecia; Pruritus; Urticaria
Musculoskeletal and connective tissue disorders	Myopathy; Muscular weakness; Osteonecrosis of femoral and humeral heads; Osteoporosis;

Table 1. Adverse Reactions	
System Organ Class	**Adverse Drug Reactions**
	Pathological fracture of long bones, postinjection flare (following intra-articular use); Growth retardation; Neuropathic arthropathy; Muscle atrophy; Myalgia; Arthralgia
Reproductive system and breast disorders	Menstruation irregular; Spermatozoa progressive motility abnormal / sperm concentration abnormal
General disorders and administration site conditions	Impaired healing; Oedema 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; Hepatomegaly; Blood urea increased; Suppression of reactions to skin tests
Injury, poisoning and procedural complications	Spinal compression fracture; Tendon rupture

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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.

9.4 Drug-Drug Interactions

CYP3A4 INHIBITORS - May decrease hepatic clearance and increase the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inhibitor, 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, 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 2 below.

Table 2 provides a list of drugs that may interact with hydrocortisone.

Table 2. Important drug or substance interactions/effects with hydrocortisone

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR Serum concentrations of isoniazid may be decreased.
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Antibiotic, Macrolides - ERYTHROMYCIN - CLARITHROMYCIN	CYP3A4 INHIBITOR (and SUBSTRATE) Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.
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, Sedatives, Hypnotics - PHENYTOIN - BARBITURATES - PHENOBARBITAL	CYP3A4 INDUCERS

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see **7 WARNINGS AND PRECAUTIONS**, **Musculoskeletal**). 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. Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.
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) Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.
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. Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
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.
Cholestyramine	Cholestyramine may increase the clearance of corticosteroids.
Estrogens (including oral contraceptives containing estrogens)	CYP3A4 INHIBITOR (and SUBSTRATE) Patients receiving both a corticosteroid and an estrogen should be observed for excessive corticosteroid effects. 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.
Hormones - SOMATROPIN	Concomitant glucocorticosteroid therapy may inhibit the response to somatropin.
Hypoglycemics	Dosage adjustments of an antidiabetic drug may be necessary when corticosteroids are given to diabetics. Corticosteroids may increase blood glucose; diabetic control should be monitored, especially when corticosteroids are initiated, discontinued, or changed in dose.
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 - TROLEANDOMYCIN	CYP3A4 INHIBITOR Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
NSAIDs - HIGH-DOSE ASA (ACETYLSALICYLIC ACID)	There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. Corticosteroids may increase the clearance of high-dose ASA, 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. ASA should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.
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.
Vaccines	Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **7 WARNINGS AND PRECAUTIONS**, **Immune, Vaccinations**).

9.5 Drug-Food Interactions

Grapefruit juice is a CYP3A4 inhibitor. See DRUG INTERACTIONS, Overview, CYP3A4 INHIBITORS above.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Corticosteroids may suppress reactions to skin tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Corticosteroids, such as glucocorticoids, bind to specific receptor proteins in target tissues to regulate the expression of corticosteroid-responsive genes, thereby changing the levels and array of proteins synthesized by the various target tissues.

10.2 Pharmacodynamics

SOLU-CORTEF contains sterile hydrocortisone sodium succinate, which is the sodium succinate ester of hydrocortisone, a glucocorticoid. Hydrocortisone sodium succinate is highly soluble, which permits the intravenous administration of high doses in a small volume of diluent. This is particularly useful in situations where high blood levels of hydrocortisone are required rapidly.

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. Following the intravenous injection of SOLU-CORTEF, experimental evidence of its effects has been noted within a few minutes and persists for a variable period. SOLU-CORTEF may be administered by intravenous infusion, or by intramuscular injection. The preferred method for initial emergency use is intravenous injection.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), 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.

The relative potency of methylprednisolone sodium succinate (SOLU-MEDROL) and hydrocortisone sodium succinate (SOLU-CORTEF), 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.

10.3 Pharmacokinetics

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 3.

Table 3. 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 3). 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 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.

Elimination
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.

11 STORAGE, STABILITY AND DISPOSAL

Store unreconstituted product at room temperature (15 - 30°C).

Store reconstituted SOLU-CORTEF at room temperature (15 - 30°C) and protect from light. Use solution only if it is clear. Discard unused solutions after 3 days.

In-house studies have shown reconstituted SOLU-CORTEF 50 mg/mL and 125 mg/mL to be physically and chemically stable after one month of freezing. Once thawed, the above guidelines should be followed for SOLU-CORTEF.

After reconstitution, SOLU-CORTEF can be diluted for intravenous infusion (see DOSAGE AND ADMINISTRATION, Intravenous infusion). Unused diluted solution should be discarded after 4 hours.

The Act-O-Vial is a single dose vial and once reconstituted solution is used, any remaining portion should be discarded.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Hydrocortisone Sodium Succinate

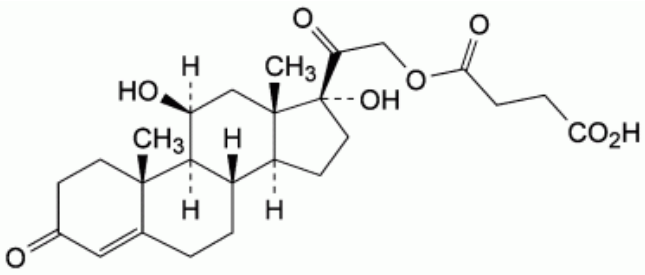
Chemical name: pregn-4-ene-3,20-dione,21-(3carboxy-l oxopropoxy)-11,17-dihydroxy-, monosodium salt, (11β)

Molecular formula: $C_{25}H_{34}O_8 \cdot H_2O$

Molecular mass: Hydrocortisone hemisuccinate: 480.56

Hydrocortisone: 362.47

Structural formula:



Physicochemical properties: white or nearly white, odorless, hygroscopic amorphous solid

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

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

Mutagenicity:
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 and Developmental Toxicology:

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 in untreated females mated with males treated at the administered doses of 10 and 25 mg/kg/day.

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSOLU-CORTEF®

Hydrocortisone sodium succinate for injection

Read this carefully before you start taking **SOLU-CORTEF** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SOLU-CORTEF**.

What is SOLU-CORTEF used for?

SOLU-CORTEF is used in adults and children:

- in the treatment of various conditions. These include allergy or inflammation;
- to replace corticosteroid hormone when the body does not produce enough. This is due to problems with the adrenal glands.
- in emergency treatment of certain conditions of shock or severe allergic reactions. SOLU-CORTEF is used when high blood levels of hydrocortisone are required quickly.

How does SOLU-CORTEF work?

SOLU-CORTEF contains corticosteroid hydrocortisone sodium succinate. Hydrocortisone belongs to a group of medicines called corticosteroids or steroids. Hydrocortisone is a hormone that decreases the body's immune response to certain diseases. This reduces symptoms such as swelling and redness.

What are the ingredients in SOLU-CORTEF?

Medicinal ingredients: Hydrocortisone sodium succinate

Non-medicinal ingredients:

Vial (powder): dibasic sodium phosphate dried and monobasic sodium phosphate anhydrous.

Vial (diluent): Sterile Water for Injection.

SOLU-CORTEF comes in the following dosage forms:

SOLU-CORTEF comes in a two-compartment Act-O-Vial system:

- upper compartment containing the sterile water (diluent)
- lower compartment containing the sterile white powder (drug): 100 mg, 250 mg, 500 mg and 1 g

Do not use SOLU-CORTEF if:

- you had an allergic reaction to hydrocortisone sodium succinate or any other corticosteroid medicine or any of the ingredients found in SOLU-CORTEF; or
- you have a fungal infection or any untreated infection.
- you have herpes simplex of the eye, except if SOLU-CORTEF is used only briefly for emergencies
- you have chickenpox or smallpox, except if SOLU-CORTEF is used only briefly for emergencies

- you have recently received a type of vaccine called a live or live / attenuated vaccine. Do not receive this vaccine during treatment with SOLU-CORTEF
- you have low platelet count and administer for intramuscular use

This medicine is not recommended for injection via the spinal cord (intrathecal or epidural)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SOLU-CORTEF. Talk about any health conditions or problems you may have, including if you:

- have or have had an infection (such as herpes simplex, chickenpox, tuberculosis, threadworm); **If you or your child is exposed to measles or chickenpox during treatment with SOLU-CORTEF, contact your healthcare professional immediately. Serious or fatal side effects can occur if you or your child have not already had these infections.**
- have recently had or are about to have any vaccination
- have bleeding problem; blood clotting problem
- have brittle bone (osteoporosis)
- have high blood pressure
- have water retention (oedema)
- have heart problems such as heart failure, heart disease or heart attack
- have kidney disease
- have diabetes
- have or have had seizures (convulsions) or other neurological problems
- have thyroid problem
- have muscle pain or weakness (such as myasthenia gravis)
- have certain eye diseases such as glaucoma, cataracts, herpes infection or any problems with the retina
- have liver disease such as cirrhosis
- have certain mental or mood conditions (such as depression)
- have or have had stomach or gut problems (ulcer, ulcerative colitis)
- have low potassium or calcium
- have a weak immune response. Tell your healthcare professional if you suspect an infection has occurred, as corticosteroids can make infections more likely and may mask their signs
- have Cushing's disease (caused by an excess of cortisol hormone)

Other warnings you should know about:

Serious Side Effects: SOLU-CORTEF can cause serious side effects, including:

- skin cancer (Kaposi's sarcoma): Kaposi's sarcoma have been reported with corticosteroid therapy, such as SOLU-CORTEF. Stopping treatment of SOLU-CORTEF may result in signs of the cancer going away.
- tumor of the adrenal glands (pheochromocytoma). This tumor has been reported with corticosteroid therapy, such as SOLU-CORTEF. Pheochromocytoma may cause death.
- fat deposition on or outside the lining of the spine (epidural lipomatosis). Taking corticosteroids in high doses for a long period of time can cause epidural lipomatosis.

Surgery: Before you have any operation, tell your doctor, dentist or anesthetist that you are taking SOLU-CORTEF.

Pregnancy and breastfeeding:

- If you are pregnant, or still able to get pregnant and/or breast-feed, there are specific risks you must discuss with your healthcare professional. Taking SOLU-CORTEF may:
    - slow the growth and cause low birth weight of the baby.
    - cause cataracts in babies. This risk is associated with mothers who take corticosteroids for a long period of time during pregnancy.
- If you are breastfeeding or planning to breastfeed, tell your healthcare professional.

Male fertility: Taking SOLU-CORTEF may affect male fertility.

Stopping treatment: If you suddenly stop taking SOLU-CORTEF, you may experience

- Serious adrenal insufficiency. Adrenal insufficiency is when the body does not make enough of the cortisol hormone. This may cause death.
- "Withdrawal syndrome". This includes symptoms such as anorexia, nausea, vomiting, lack of energy, headache, fever, joint pain, peeling of skin, muscle pain, weight loss, and/or low blood pressure.

Immunosuppression:

- SOLU-CORTEF may:
    - hide symptoms of infection
    - reactivate dormant infections
    - cause infections due to lowered body resistance
- Tell your healthcare professional you are taking SOLU-CORTEF since it can affect the results of skin tests

Driving and Using Machines: SOLU-CORTEF may cause dizziness (vertigo), tiredness or blurred vision. Be careful about driving or doing activities that require you to be alert. If you experience these symptoms after taking SOLU-CORTEF, do NOT drive or operate machinery.

Children (less than 18 years of age):

- Children may experience a decrease in the speed of their growth. The healthcare provider will prescribe the lowest dose to minimize this risk.
- The healthcare professional will conduct frequent tests on the child if they are taking SOLU-CORTEF for a long period of time. Taking hydrocortisone for a long period of time increases the risk of developing a high intracranial pressure (growing pressure in skull).
- If hydrocortisone is given to a prematurely born baby, monitoring of the heart may be needed.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SOLU-CORTEF:

- Medicines used to:
    - "thin" the blood (anticoagulants)

- treat myasthenia gravis a muscle condition
- treat bacterial infection (such as erythromycin, clarithromycin and troleandomycin)
- treat fungal infections (such as ketoconazole and itraconazole)
- treat inflammatory conditions (such as methylprednisolone)
- treat epilepsy (such as barbiturates, carbamazepine, phenobarbital and phenytoin)
- treat heart problems or high blood pressure (such as calcium channel blockers, diltiazem and digoxin)
- treat high cholesterol (cholestyramine)
- reduce extra fluid in the body (diuretics)
- treat HIV infections (such as indinavir or ritonavir)
- treat high blood sugar (diabetes)
- treat tuberculosis (such as isoniazid, and rifampin)
- to prevent or alleviate nausea and vomiting (such as aprepitant or fosaprepitant)
- treat breast or ovarian cancer (aromatase inhibitors)
- suppress or reduce the strength of the body's immune system (such as cyclosporine, cyclophosphamide, and tacrolimus which are used to help prevent organ rejection or treat cancer)
- aspirin and non-steroidal anti-inflammatory drugs
- vaccines
- hormones (such as estrogen and somatropin)
- potassium depleting agents

Do not drink grapefruit juice while taking Solu-Cortef.

How to take SOLU-CORTEF:

- SOLU-CORTEF will be given to you by your healthcare professional. They will decide to give SOLU-CORTEF to you by either:
  - into your vein (intravenous injection or infusion); or
  - into your muscle (intramuscular).
- Your healthcare professional will decide on the site of injection, as well as how much of the medicine and how many injections you will receive.
- SOLU-CORTEF should not be stopped abruptly. Do not stop taking SOLU-CORTEF without talking to your healthcare professional. You will need to come off this medicine slowly to avoid withdrawal symptoms.
- The healthcare professional will prescribe the lowest possible dose for the minimum period of time.

Usual dose:

- The dose depends on the:
  - type of condition being treated;
  - severity of the condition;
  - response to the treatment, and
  - your exposure to stress

Overdose:

If you think you, or a person you are caring for, have taken too much SOLU-CORTEF, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you are concerned that you, or a person you are caring for, may have missed a dose, talk to your healthcare professional immediately.

What are possible side effects from using SOLU-CORTEF?

These are not all the possible side effects you may have when taking SOLU-CORTEF. If you experience any side effects not listed here, tell your healthcare professional.

Potential side effects may include:

Skin problems:

- thin fragile skin
- ecchymosis (spots caused by ruptured blood vessels)
- petechiae (reddish spot containing blood that appears in skin)
- stretch marks
- dry, scaly skin
- rash
- redness
- itching
- hives
- abscess

Hormone and metabolism problems:

- development of Cushingoid state (abnormal bodily condition caused by excess corticosteroids)
- moon face (enlargement of chin and forehead)
- weight gain
- abnormal fat deposits
- hypopituitarism (a condition in which your pituitary gland fails to produce one or more of its hormones or does not produce enough of them).
- abnormal hair growth
- thinning hair
- acne
- increased sweating
- lightening or darkening of an area of skin
- thyroid gland problems

Stomach and intestinal problems:

- nausea
- vomiting
- altered sense of taste (with rapid administration of large doses)
- abdominal pain
- bloating
- diarrhea
- indigestion
- increased appetite

Musculoskeletal problems:

- loss of muscle mass
- muscle pain
- malaise (feeling of general discomfort or uneasiness)

Nervous system problems:

- headache
- dizziness
- amnesia
- vertigo
- impaired sensation, strength, and reflexes

- sensation of tingling, tickling, prickling, or burning of a person's skin

Psychiatric problems:

- anxiety
- confusion
- hallucination
- emotional instability
- euphoria (intense feelings of well-being, elation, happiness, excitement and joy)
- mood swings
- personality changes
- drug dependence
- mania
- delusion
- schizophrenia
- abnormal behavior
- irritability

Other:

- high cholesterol
- fatigue
- hiccups
- injection site reaction
- injection site scarring (dent/hole)

SOLU-CORTEF can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Heart failure: Shortness of breath, fatigue, weakness, dizziness, irregular heart beat			√
Blood clots: swelling, pain or tenderness, usually in the arm or leg		√	
Liver enlargement: jaundice (yellowing of the skin or whites of eyes), urine turns dark, nausea, vomiting, lower stomach pain		√	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen		√	
Fluid retention, swelling		√	
High blood pressure: headaches or feeling unwell			√
Muscle weakness			√
Stomach ulcers (burst or bleeding ulcers): stomach pain, blood in stools and/or vomiting blood			√
Wounds that are slow to heal	√		
Convulsions			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Psychological disorders: feeling depressed including thinking about suicide, feeling anxious, insomnia		√	
Irregular menstrual periods	√		
Diabetes: frequent urination, hunger and thirst		√	
Cramps and spasms		√	
Visual problems: failing eyesight, blurry vision, eye pain, increased pressure in your eyes		√	
Reactivation of tuberculosis: coughing blood or pain in the chest)			√
Infections: raised temperature and feeling unwell.			√
Osteoporosis (thin, fragile bones) bone/joint pain, broken bones, back pain that gets worse when standing or walking			√
Allergic reactions: rash, hives, swelling of the face, lips, tongue or throat. Difficulty swallowing or breathing			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Before Reconstitution: Store SOLU-CORTEF at room temperature (15° C to 30°C).

After Reconstitution: Store reconstituted SOLU-CORTEF at room temperature (15° C to 30°C) and protect from light. Use solution only if it is clear. Discard unused solution after 3 days. Reconstituted SOLU-CORTEF can also be frozen for up to 1 month. Once thawed, the above guidelines should be followed for SOLU-CORTEF.

SOLU-CORTEF can be diluted for intravenous infusion. Unused diluted solution should be discarded after 4 hours.

After Dilution for Intravenous Infusion: Discard unused solution after 4 hours

Single use vial, discard after use.

Keep out of reach and sight of children.

If you want more information about SOLU-CORTEF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.pfizer.ca, or by calling 1-800-463-6001.

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