

PRODUCT MONOGRAPH

Pr SOLU-CORTEF* Act-O-Vials†

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 Inc.
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Kirkland, Québec H9J 2M5

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3

 SUMMARY PRODUCT INFORMATION 3

 INDICATIONS AND CLINICAL USE..... 3

 CONTRAINDICATIONS 6

 WARNINGS AND PRECAUTIONS..... 6

 ADVERSE REACTIONS 14

 DRUG INTERACTIONS..... 17

 DOSAGE AND ADMINISTRATION..... 22

 OVERDOSAGE 25

 ACTION AND CLINICAL PHARMACOLOGY 25

 STORAGE AND STABILITY 26

 DOSAGE FORMS, COMPOSITION AND PACKAGING 27

PART II: SCIENTIFIC INFORMATION 28

 TOXICOLOGY 28

PART III: CONSUMER INFORMATION..... 29

SOLU-CORTEF Act-O-Vials

Sterile Powder

Hydrocortisone sodium succinate for injection USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal 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 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

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
- Seasonal or perennial allergic rhinitis
- 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 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.

CONTRAINDICATIONS

SOLU-CORTEF (hydrocortisone sodium succinate) is contraindicated:

- in patients with known hypersensitivity to any components of the product;
- 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 (diluent 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.

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 physicians 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 TOXICOLOGY, Mutagenesis).

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.

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 reinstated. If the patient is currently receiving corticosteroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid 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 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 CONTRAINDICATIONS; 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.

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 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.

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 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.

Sensitivity

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 ADVERSE REACTIONS).

Sexual Function/Reproduction

Steroids may increase or decrease motility and number of spermatozoa in some patients (see TOXICOLOGY).

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.

Special Populations

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.

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 labour and delivery.

Nursing Women

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.

Pediatrics

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.

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.

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.

ADVERSE REACTIONS

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
<i>Infections and infestations</i>	Opportunistic infection; Infection; Infection susceptibility increased
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
<i>Blood and lymphatic system disorders</i>	Leukocytosis
<i>Immune system disorders</i>	Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction
<i>Endocrine disorders</i>	Cushingoid; Hypopituitarism; Hirsutism; Hypertrichosis; Abnormal fat deposits; Weight increased; Moon face; Glycosuria; Steroid withdrawal syndrome
<i>Metabolism and nutrition disorders</i>	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)
<i>Psychiatric disorders</i>	Affective disorder (including depression, euphoric mood, affect lability, drug dependence, suicidal ideation);

Table 1. Adverse Reactions	
System Organ Class	Adverse Drug Reactions
	Psychotic disorder (including mania, delusion, hallucination and schizophrenia); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behavior; Insomnia; Irritability
<i>Nervous system disorders</i>	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
<i>Eye disorders</i>	Cataract; Exophthalmos; Glaucoma; Rare instances of blindness associated with periocular injections; Central serous chorioretinopathy
<i>Ear and labyrinth disorders</i>	Vertigo
<i>Cardiac disorders</i>	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);

Table 1. Adverse Reactions	
System Organ Class	Adverse Drug Reactions
	Pulmonary oedema; Syncope; Tachycardia; Embolism; Thrombophlebitis; Vasculitis
<i>Vascular disorders</i>	Hypertension; Hypotension; Thrombosis
<i>Respiratory, thoracic and mediastinal disorders</i>	Pulmonary embolism; Hiccups
<i>Gastrointestinal disorders</i>	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)
<i>Skin and subcutaneous tissue disorders</i>	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;

Table 1. Adverse Reactions	
System Organ Class	Adverse Drug Reactions
	Rash; Abscess sterile; Skin striae; Alopecia; Pruritus; Urticaria
<i>Musculoskeletal and connective tissue disorders</i>	Myopathy; Muscular weakness; Osteonecrosis of femoral and humeral heads; Osteoporosis; Pathological fracture of long bones, postinjection flare (following intra-articular use); Growth retardation; Neuropathic arthropathy; Muscle atrophy; Myalgia; Arthralgia
<i>Reproductive system and breast disorders</i>	Menstruation irregular; Spermatozoa progressive motility abnormal / sperm concentration abnormal
<i>General disorders and administration site conditions</i>	Impaired healing; Oedema peripheral; Fatigue; Malaise; Injection site reaction
<i>Investigations</i>	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
<i>Injury, poisoning and procedural complications</i>	Spinal compression fracture; Tendon rupture

DRUG INTERACTIONS

Overview

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

steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

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)

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
Anticonvulsants, Sedatives, Hypnotics - PHENYTOIN - BARBITURATES - PHENOBARBITAL	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	<p>Corticosteroids may influence the effect of anticholinergics.</p> <p>An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see WARNINGS AND PRECAUTIONS, Musculoskeletal).</p> <p>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.</p>
Anticholinesterases	<p>Steroids may reduce the effects of anticholinesterases in myasthenia gravis.</p> <p>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.</p>
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	<p>CYP3A4 INHIBITORS (and SUBSTRATES)</p> <p>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.</p>
Antivirals - HIV-PROTEASE INHIBITORS	<p>CYP3A4 INHIBITORS (and SUBSTRATES)</p> <p>1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.</p> <p>2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.</p>

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
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)
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.
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE) Patients receiving both a corticosteroid and an estrogen should be observed for excessive corticosteroid effects.
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)	<p>There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs.</p> <p>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.</p>
Potassium Depleting Agents	<p>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.</p>
Vaccines	<p>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 WARNINGS AND PRECAUTIONS, Immune, Vaccinations).</p>

Drug-Food Interactions

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

Drug-Laboratory Interactions

Corticosteroids may suppress reactions to skin tests.

Drug-Lifestyle Interactions

Ability to drive and use 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage requirements are variable and must be individualized. 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. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains 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 is recommended that it be withdrawn gradually.

Recommended Dosage 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 WARNINGS AND PRECAUTIONS) and reduced dosing may be considered.

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.

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.

Special Populations

Pediatrics

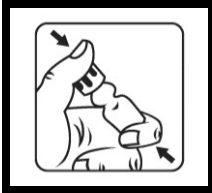
Dosing in infants and children is governed more by the severity of the condition and response of the patient than by age or body weight. The daily dose should be not less than 25 mg.

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.

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

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



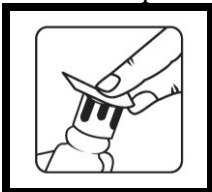
2. Gently agitate to effect solution.



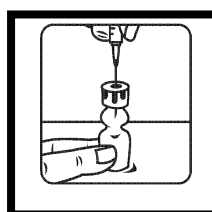
3. Remove plastic tab covering center of stopper.



4. Sterilize top of stopper with a suitable germicide.



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



- Invert vial and withdraw dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

ACTION AND CLINICAL PHARMACOLOGY

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.

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

Hydrocortisone is also metabolized by CYP3A4 to 6 β -hydroxycortisol (6 β -OHF), and 6 β -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.

STORAGE AND STABILITY

Store unconstituted 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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.

PART II: SCIENTIFIC INFORMATION

TOXICOLOGY

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. Fludrocortisone (9 α -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 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.

PART III: CONSUMER INFORMATION

PrSOLU-CORTEF[®] Act-O-Vials[†]
Hydrocortisone sodium succinate for injection

This leaflet is Part III of a three-part “Product Monograph” published when SOLU-CORTEF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SOLU-CORTEF[®]. Contact your doctor or pharmacist if you have any questions about this drug.

ABOUT THIS MEDICATION

What the medication is used for:

SOLU-CORTEF is used

- in the treatment of various conditions such as allergy or inflammation;
- to replace corticosteroid hormone when the body does not produce enough due to problems with the adrenal glands.
- in emergency treatment of certain conditions of shock or severe allergic reactions, where high blood levels of hydrocortisone are required rapidly.

What it does:

SOLU-CORTEF contains a corticosteroid hormone. This hormone decreases the body’s immune response to certain diseases and reduces symptoms such as swelling and redness

When it should not be used:

Do not use SOLU-CORTEF if you have:

- had an allergic reaction to hydrocortisone or any other steroid medicine or any of the ingredients found in SOLU-CORTEF; or
- a fungal infection or any untreated infection.
- herpes simplex of the eye, except if SOLU-CORTEF is used only briefly for emergencies
- chickenpox or smallpox
- received a type of vaccine called a live or live / attenuated vaccine
- low platelet count

What the medicinal ingredient is:

Hydrocortisone sodium succinate.

What the nonmedicinal ingredients are:

Lower vial: dibasic sodium phosphate dried and monobasic sodium phosphate anhydrous.

Upper vial: Sterile Water for Injection.

What dosage forms it comes in:

SOLU-CORTEF comes in a two-compartment Act-O-Vial system: a clear vial containing sterile white powder (the drug) in the lower compartment and sterile water in the upper

compartment. It is available in 4 strengths:
100 mg / 2mL water Act-O-Vials
250 mg / 2mL water Act-O-Vials
500 mg / 4mL water Act-O-Vials
1000 mg / 8mL water Act-O-Vials

WARNINGS AND PRECAUTIONS

Before taking SOLU-CORTEF, talk to your doctor or pharmacist 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 doctor immediately.**
- you have recently had or are about to have any vaccination
- you have bleeding problem; blood clotting problem
- you have brittle bone (osteoporosis)
- you have high blood pressure
- you have heart problems such as heart failure
- you have kidney disease
- you have diabetes
- you have or have had seizures (convulsions) or other neurological problems
- you have thyroid problem
- you have muscle pain or weakness (such as myasthenia gravis)
- you have skin cancer (Kaposi’s sarcoma), or a tumor of the adrenal glands (pheochromocytoma)
- you have certain eye diseases such as glaucoma, cataracts, herpes infection or any problems with the retina
- you have liver disease such as cirrhosis
- you have certain mental or mood conditions (such as depression)
- you have or have had stomach or gut problems (ulcer, ulcerative colitis)
- you have low potassium or calcium
- you have a weak immune response
- you have Cushing’s disease (caused by an excess of cortisol hormone)
- you are pregnant or trying to become pregnant
- you are breast-feeding or planning to breast-feed

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

INTERACTIONS WITH THIS MEDICATION

Before taking SOLU-CORTEF, please talk to your doctor or pharmacist about all your other medications including those you bought without prescription, herbal or natural product and especially if are taking the following:

- drugs to treat glaucoma and epilepsy (such as acetazolamide)
- drugs to “thin” the blood (anticoagulants such as warfarin, coumadin)
- drugs to treat myasthenia gravis a muscle condition (such as distigmine and neostigmine)
- antibiotics (erythromycin, clarithromycin and troleandomycin, rifampicin and rifabutin)
- aspirin and non steroidal anti-inflammatory drugs (such as ibuprofen)
- drugs to treat inflammatory conditions (such as methylprednisolone)
- drugs to treat epilepsy (such as barbiturates and phenytoin)
- drugs for antifungal infections (such as ketoconazole)
- cyclosporine
- drugs for heart problems or high blood pressure (such as calcium channel blockers, diltiazem and digoxin)
- drugs to treat high cholesterol (cholestyramine)
- water pills (diuretics)
- drugs to treat HIV infections (such as indinavir or ritonavir)
- vaccines
- hormones, (such as estrogen and somatropin)
- drugs to treat diabetes
- drugs to treat tuberculosis
- drugs to prevent or alleviate nausea and vomiting (such as aprepitant or fosaprepitant)
- aromatase inhibitors (drugs to treat breast or ovarian cancer)
- immunosuppressants (drugs that suppress or reduce the strength of the body's immune system)
- potassium depleting agents

Do not drink grapefruit juice while taking Solu-Cortef.

PROPER USE OF THIS MEDICATION

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

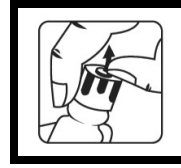
1. Press down on plastic activator to force sterile water into the lower compartment.



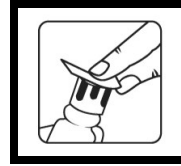
2. Gently agitate to effect solution.



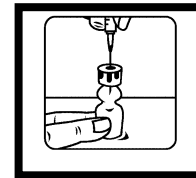
3. Remove plastic tab covering center of stopper.



4. Sterilize top of stopper with a suitable germicide.



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



6. Invert vial upside-down and withdraw dose.

Usual dose:

The initial dose of SOLU-CORTEF depends on the type of condition and the severity of the condition. Your doctor will decide on the site of injection, as well as how much of the medicine and how many injections you will receive.

A medical professional can also administer diluted SOLU-CORTEF as an intravenous infusion.

SOLU-CORTEF can affect growth in children so your doctor will prescribe the lowest dose that will be effective for your child.

When your condition has improved, your dose will be reduced gradually.

SOLU-CORTEF should not be stopped abruptly. Do not stop taking SOLU-CORTEF without talking to your doctor.

Overdose:

In case of drug overdose, contact your doctor, or a poison control centre, or go to emergency room of the hospital near you immediately, even if there are no symptoms

Missed Dose:

If you are concerned that you may have missed a dose, talk to you doctor or nurse immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following is a list of side effects that may occur with SOLU-CORTEF. This is not a complete list. Therefore, check with your doctor immediately if you notice or are bothered by any unusual symptoms.

SOLU-CORTEF may hide symptoms of infections, may cause latent infections to become active, and may induce infections by normally inoffensive organisms due to lowered body resistance.

Potential side effects of SOLU-CORTEF include:

Allergic Reactions:

- anaphylaxis (a severe, life-threatening allergic reaction)
- cardiac arrest
- bronchospasm (narrowing of the airway)

Cardiovascular:

- heart failure
- heart attack
- arrhythmia (irregular heartbeat)
- high or low blood pressure
- blood clots
- thrombophlebitis (vein inflammation)
- thrombosis (blood clot within a blood vessel)
- high cholesterol

Dermatologic:

- thin fragile skin
- impaired wound healing
- swelling
- 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
- acne
- increased sweating
- lightening or darkening of an area of skin
- abscess
- suppressed reactions to skin tests
- thinning hair

Endocrine and Metabolism:

- 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).

- suppression of growth in children
- abnormal hair growth
- new symptoms of diabetes
- thyroid gland problems

Gastrointestinal:

- stomach ulcer
- stomach bleeding
- inflammation of the pancreas and esophagus
- perforation of the bowel
- nausea
- vomiting or altered sense of taste (with rapid administration of large doses)
- abdominal pain
- bloating
- diarrhea
- indigestion
- bowel/bladder dysfunction
- increased appetite

Hepatic:

- enlarged liver

Pancreatic:

- Pancreatitis (inflammation of the pancreas)

Musculoskeletal:

- loss of muscle mass
- muscle weakness
- muscle pain
- malaise (feeling of general discomfort or uneasiness)
- osteoporosis
- pathological fractures
- vertebral compression fractures
- tendon rupture
- Charcot joint disease (neuropathic arthropathy)
- joint pain

Neurologic:

- seizures
- headache
- dizziness
- amnesia
- vertigo
- pain and tenderness
- impaired sensation, strength, and reflexes
- sensation of tingling, tickling, prickling, or burning of a person's skin

Ophthalmologic:

- cataracts
- increased intraocular pressure
- glaucoma

Psychiatric:

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

Sexual Function/Reproduction:

- menstrual irregularities
- increased or decreased motility and number of sperm

Hematology:

- above normal white blood cell count
- abnormal blood tests

Other:

- fatigue
- hiccups
- injection site reaction

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Congestive heart failure			√
Fluid retention, swelling		√	
High blood pressure (symptoms of which are headaches or feeling unwell)			√
Muscle weakness			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Stomach ulcers (burst or bleeding ulcers; symptoms of which are stomach pain, blood in stools and/or vomiting blood)			√
Wounds that are slow to heal	√		
Convulsions			√
Psychological disorders (feeling depressed including thinking about suicide, feeling anxious, insomnia)		√	
Irregular menstrual periods	√		
Diabetes (symptoms of which can be frequent urination and thirst)		√	
Cramps and spasms		√	
Visual problems, failing eyesight		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Reactivation of tuberculosis (symptoms of which could be coughing blood or pain in the chest)			√
Infections (symptoms might include a raised temperature and feeling unwell)			√
Bone/joint pain			√
Bone thinning			√
Allergic reactions in the form of angioedema (a severe skin reaction with swelling, itching and large welts).			√

This is not a complete list of side effects. For any unexpected effects while taking SOLU-CORTEF contact your doctor or pharmacist.

HOW TO STORE IT

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

After Reconstitution: Store reconstituted solution of SOLU-CORTEF at room temperature (15° C to 30°C). Protect from light. Discard unused solution after 3 days. Reconstituted SOLU-CORTEF can also be frozen for up to 1 month.

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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at: <http://www.pfizer.ca> or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001.

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