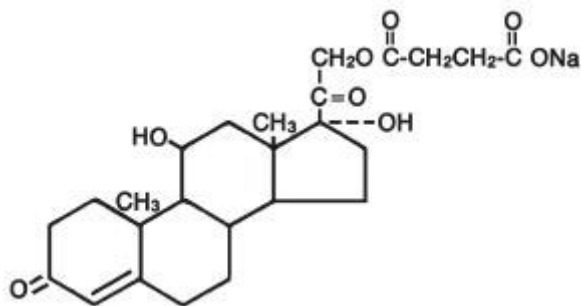

Solu-Cortef®

hydrocortisone sodium succinate
for injection, USP

For Intravenous or Intramuscular Administration**DESCRIPTION**

SOLU-CORTEF Sterile Powder contains hydrocortisone sodium succinate as the active ingredient. Hydrocortisone sodium succinate is a white or nearly white, odorless, hygroscopic amorphous solid. It is very soluble in water and in alcohol, very slightly soluble in acetone and insoluble in chloroform. The chemical name is pregn-4-ene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-, monosodium salt, (11β)- and its molecular weight is 484.52.

The structural formula is represented below:



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

SOLU-CORTEF Sterile Powder is available in several packages for intravenous or intramuscular administration.

100 mg Plain—Vials containing hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone, also 0.8 mg monobasic sodium phosphate anhydrous, 8.73 mg dibasic sodium phosphate dried. SOLU-CORTEF 100 mg plain does not contain diluent (see DOSAGE and ADMINISTRATION, Preparation of Solutions).

ACT-O-VIAL[®] System (Single-Dose Vial) in four strengths:

| | 100 mg | 250 mg | 500 mg | 1000 mg |
|--------------------------------------|----------------|----------------|----------------|----------------|
| | ACT-O-VIAL | ACT-O-VIAL | ACT-O-VIAL | ACT-O-VIAL |
| | Each 2 mL | Each 2 mL | Each 4 mL | Each 8 mL |
| | contains: | contains: | contains: | contains: |
| | (when mixed) | (when mixed) | (when mixed) | (when mixed) |
| Hydrocortisone | equiv. to | equiv. to | equiv. to | equiv. to |
| sodium succinate | 100 mg | 250 mg | 500 mg | 1000 mg |
| | Hydrocortisone | Hydrocortisone | Hydrocortisone | Hydrocortisone |
| 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 |
| Benzyl alcohol added as preservative | 18.1 mg | 16.4 mg | 33.4 mg | 66.9 mg |

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8.

ACTIONS

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

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

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 hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injection.

INDICATIONS

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the

condition, SOLU-CORTEF Sterile Powder is indicated for intravenous or intramuscular use in the following conditions:

1. Endocrine Disorders

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

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

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

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

Congenital adrenal hyperplasia

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

Acute and subacute bursitis

Synovitis of osteoarthritis

Epicondylitis

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

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

Bullous dermatitis herpetiformis

Severe erythema multiforme (Stevens-Johnson syndrome)

Severe seborrheic dermatitis

Severe psoriasis

Exfoliative dermatitis

Mycosis fungoides

5. Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma

Drug hypersensitivity reactions

Contact dermatitis

Urticarial transfusion reactions

Atopic dermatitis

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)

Serum sickness

Seasonal or perennial allergic rhinitis

6. Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

- | | |
|---|----------------------------------|
| Herpes zoster ophthalmicus | Sympathetic ophthalmia |
| Iritis, iridocyclitis | Anterior segment inflammation |
| Chorioretinitis | Allergic conjunctivitis |
| Diffuse posterior uveitis and choroiditis | Allergic corneal marginal ulcers |
| Optic neuritis | 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 Loeffler's syndrome not manageable
Berylliosis by other means
Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy Aspiration pneumonitis
- 9. Hematologic Disorders**
Acquired (autoimmune) hemolytic anemia Erythroblastopenia (RBC anemia)
Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated) 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. Nervous System**
Acute exacerbations of multiple sclerosis
- 13. Miscellaneous**
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS

The use of SOLU-CORTEF Sterile Powder is contraindicated in premature infants because the 100 mg, 250 mg, 500 mg and 1000 mg ACT-O-VIAL System contain benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. SOLU-CORTEF Sterile Powder is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS

Exposure to excessive amounts of benzyl alcohol has been associated with increased toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare

reports of deaths, primarily in pre-term infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is unknown. If the patient requires more than the recommended dosages of other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS, Pediatric Use**).

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids 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 of 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.¹

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.²

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Results from one multicenter, randomized, placebo controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including SOLU-CORTEF, should not be used for the treatment of traumatic brain injury.

Usage in pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

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 the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of SOLU-CORTEF Sterile Powder 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 antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions (e.g., bronchospasm) have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. 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.

PRECAUTIONS

General precautions

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol

and its metabolites found in the blood and urine), has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, Bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Pre-mature and low-birth-weight infants, as well as patients receiving high doses, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. 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 and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

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.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

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

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies

do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. 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 effect.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

| | |
|--|-----------------------|
| Sodium retention | Potassium loss |
| Fluid retention | Hypokalemic alkalosis |
| Congestive heart failure in susceptible patients | Hypertension |

Musculoskeletal

| | |
|------------------|---------------------------------|
| Muscle weakness | Vertebral compression fractures |
| Steroid myopathy | Aseptic necrosis of femoral |

Loss of muscle mass
Osteoporosis
Tendon rupture, particularly of the
Achilles tendon

and humeral heads
Pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible
perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis

Increases in alanine transaminase
(ALT, SGPT), aspartate transaminase
(AST, SGOT) and alkaline phosphatase
have been observed following
corticosteroid treatment. These changes
are usually small, not associated with
any clinical syndrome and are
reversible upon discontinuation.

Dermatologic

Impaired wound healing
Thin fragile skin
Petechiae and ecchymoses

Facial erythema
Increased sweating
May suppress reactions to skin tests

Neurological

Convulsions
Increased intracranial pressure
with papilledema (pseudotumor
cerebri) usually after treatment

Vertigo
Headache

Endocrine

Menstrual irregularities
Development of Cushingoid state
Suppression of growth in children
Secondary adrenocortical and
pituitary unresponsiveness,
particularly in times of stress, as
in trauma, surgery, or illness

Decreased carbohydrate tolerance
Manifestations of latent diabetes
mellitus
Increased requirements of insulin
or oral hypoglycemic agents in
diabetics

Ophthalmic

Posterior subcapsular cataracts
Increased intraocular pressure

Glaucoma
Exophthalmos

Metabolic

Negative nitrogen balance due to
protein catabolism

The following additional reactions are related to parenteral corticosteroid therapy:

Allergic, anaphylactic or
other hypersensitivity

Subcutaneous and cutaneous
atrophy

reactions
Hyperpigmentation or
hypopigmentation

Sterile abscess

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS)

This preparation may be administered by intravenous injection, by intravenous infusion, or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

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

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

The initial dose of SOLU-CORTEF Sterile Powder is 100 mg to 500 mg, depending on the severity of the condition. This dose may be repeated at intervals of 2, 4 or 6 hours as indicated by the patient's response and clinical condition. While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily.

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

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

Preparation of Solutions

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

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

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

REFERENCES

1. Fekety R. Infections associated with corticosteroids and immunosuppressive therapy. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. Philadelphia: WBSaunders Company 1992:1050-1.
2. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticoids. *Rev Infect Dis* 1989;11(6):954-63.

Rx only



Distributed by

Pharmacia & Upjohn Company

Division of Pfizer Inc, NY, NY 10017

LAB-0121-5.0

Revised May 2008