1.0 PHARMACOLOGIC CATEGORY

Corticosteroid

2.0 DESCRIPTION

Solu-Cortef (hydrocortisone sodium succinate or pregn-4-ene-3.20-dione, 21-(3-carboxy-1-oxopropoxy)-11, 17-dihydroxy; monosodium salt, (11β) is an anti-inflammatory adrenocortical steroid. This highly water soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly.

The structural formula is represented below:

![Structural formula of hydrocortisone sodium succinate](image)

When necessary the pH of Solu-Cortef was adjusted with Sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8.

3.0 FORMULATION

Solu-Cortef 100 mg Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone

Solu-Cortef 100 mg/2 mL Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone/2 mL

Solu-Cortef 250 mg/2 mL Sterile Powder for Injection (IM/IV) contains hydrocortisone sodium succinate equivalent to 250 mg hydrocortisone/2 mL.

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

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency
Acute adrenocortical insufficiency
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. Non-endocrine Disorders

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

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

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

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

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

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

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

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

**Neoplastic Diseases** — For palliative management of:
- Acute leukemia of childhood
- Leukemias and lymphomas in adults

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

**Medical Emergencies**

Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present.

Acute allergic disorders (status asthmaticus, anaphylactic reactions, insect stings, etc) following epinephrine.

Although there are no well controlled (double-blind, placebo) clinical trials, data from experimental animal models indicate that corticosteroids may be useful in hemorrhagic, traumatic
and surgical shock in which standard therapy (e.g., fluid replacement) has not been effective (see 4.4 Special Warnings and Precautions for Use).

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

### 4.2 Dosage and Method of Administration

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

Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Therapy is initiated by administering the drug intravenously over a period of 30 seconds (e.g., hydrocortisone sodium succinate equivalent to 100 mg of hydrocortisone) to 10 minutes (e.g., 500 mg or more). 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 corticosteroid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

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

The initial dose is 100 mg to 500 mg or more (hydrocortisone equivalent of hydrocortisone sodium succinate) depending on the severity of the condition.

This dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient’s responses and clinical condition. While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily. Patients subjected to severe stress following corticosteroid therapy should be observed closely for signs and symptoms of adrenocortical insufficiency.

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

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

**Preparation of Solutions**

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

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

Directions for using Act-O-Vial Two-Compartment Vial
1. Remove protective cap, give the plunger-stopper a quarter-turn and press to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Sterilize top of plunger-stopper with a suitable germicide.
4. Insert needle squarely through center of plunger-stopper until tip is just visible (as illustrated). Invert vial and withdraw dose.

Further dilution is not necessary for intravenous or intramuscular injection. For intravenous infusion, first prepare solution as just described. The 100 mg solution may then be added to 100 to 1000 mL of 5% dextrose in Water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction). The 250 mg solution may be added to 250 to 1000 mL, the 500 mg solution may be added to 500 to 1000 mL, and the 1000 mg solution to 1000 mL of the same diluents. In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg (hydrocortisone equivalent of hydrocortisone sodium succinate) may be added to 50 mL of the above diluents. The resulting solutions are stable for at least 4 hours and may be administered either directly or by IV “piggy-back.”

4.3 Contraindications

Systemic fungal infections.

Known hypersensitivity to the drug or any component of the formulation. Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

4.4 Special Warnings and Precautions for Use

In patients on corticosteroid therapy subjected to unusual stress, increased dosage or 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 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.
The use of hydrocortisone sodium succinate in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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 immnosuppressive 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.

Hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

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.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal “Gasping Syndrome” in premature infants.

Although recent studies have not been conducted with hydrocortisone or other corticosteroids, studies of methylprednisolone sodium succinate in septic shock suggest that increased mortality may occur in some subgroups of patients at higher risk (i.e., elevated creatinine greater than 2.0 mg% or with secondary infections).

Hydrocortisone may have an increased effect in patients with liver disease since the metabolism and elimination of hydrocortisone is significantly decreased in these patients.

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

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

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 infections, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

An acute myopathy has been described with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., 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.

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

4.5 **Interaction with other Medicinal Products and Other Forms of Interaction**

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 anticoagulant when given concurrently with corticosteroids. Therefore coagulation indices should be monitored to maintain the desired anticoagulant effect.

4.6 **Fertility, Pregnancy and Lactation**

Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. Adequate human reproductive studies have not been done with corticosteroids. Therefore the use of this drug in pregnancy, nursing mothers, or women of childbearing potential requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or fetus. Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy only if clearly needed.

Corticosteroids readily cross the placenta. 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.

Corticosteroids are excreted in breast milk.

There is no evidence that corticosteroids are carcinogenic, mutagenic or impair fertility.

4.7 **Effects on Ability to Drive and Use Machines**

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

4.8 **Undesirable Effects**

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

Sodium retention
Congestive heart failure in susceptible patients
Hypertension
Fluid retention
Potassium loss
Hypokalemic alkalosis
Increased calcium excretion

Musculoskeletal
Steroid myopathy
Muscle weakness
Osteoporosis
Pathologic fractures
Vertebral compression fractures
Aseptic necrosis
Tendon rupture, particularly of the Achilles tendon

Gastrointestinal
Peptic ulceration with possible perforation and hemorrhage
Gastric hemorrhage
Pancreatitis
Esophagitis
Perforation of the bowel
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
Petechiae and ecchymosis
Thin fragile skin
Kaposi’s sarcoma has been reported to occur in patients receiving corticosteroid therapy.

Metabolic
Negative nitrogen balance due to protein catabolism

Neurological
Increased intracranial pressure
Psuedotumor cerebri
Psychic derangements/psychotic manifestations including euphoria, insomnia, mood swings, personality changes, depression; exacerbation of preexisting emotional instability or psychotic tendencies
Seizures

Endocrine
Menstrual irregularities
Development of Cushingoid state
Suppression of pituitary-adrenal axis
Decreased carbohydrate tolerance
Manifestations of latent diabetes mellitus
Increased requirements of insulin or oral hypoglycemic agents in diabetics
Suppression of growth in children
Ophthalmic
Posterior subcapsular cataracts
Increased intraocular pressure
Exophthalmics

Immune System
Masking of infections
Latent infections becoming active, including reactivation of tuberculosis
Opportunistic infections with any pathogen, in any location in the body from mild to fatal
Hypersensitivity reactions including anaphylaxis and anaphylactoid reactions (e.g. bronchospasm, laryngeal edema, urticaria)
May suppress reactions to skin tests

Miscellaneous
This product contains benzyl alcohol which has been associated with a fatal "GASping Syndrome" in premature infants.

4.9 Overdose

There is no clinical syndrome of acute overdosage with hydrocortisone sodium succinate. Hydrocortisone is dialyzable.

5.0 PHARMACEUTICAL PARTICULARS

5.1 Shelf Life

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

5.2 Special Precautions for Storage

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

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

Keep out of reach of children.

5.3 Availability

100 mg vial x 1’s
100 mg ACT-O-VIAL x 1’s
250 mg ACT-O-VIAL x 1’s
500 mg ACT-O-VIAL x 1’s

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

Manufactured by:
PHARMACIA & UPJOHN COMPANY
7000 Portage Road,
Kalamazoo, Michigan, USA

Imported by: