SOLU CORTEF® 100 MG

NAME OF THE MEDICINAL PRODUCT

SOLU CORTEF® 100 MG

QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in SOLU CORTEF® is hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone.

For the full list of excipients, see section "**DESCRIPTION**" below.

PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

For Intravenous or Intramuscular Administration

DESCRIPTION

SOLU CORTEF® Sterile Powder is an anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as the active ingredient. SOLU CORTEF® is available in several packages for intravenous or intramuscular administration.

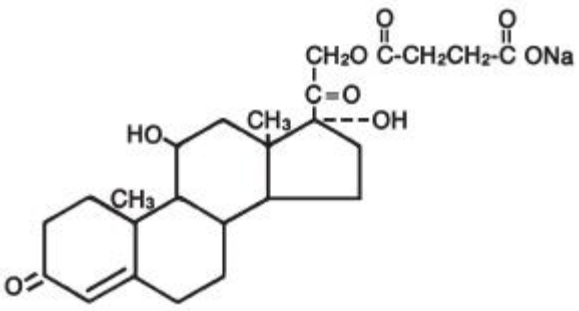
100 mg Plain Vial
Each vial contains Hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone.
Monobasic sodium phosphate monohydrate 0.9 mg
Dibasic sodium phosphate dried 8.8mg
Sodium Hydroxide
Water for injections

SOLU CORTEF® 100 mg plain does not contain diluent (see **DOSAGE AND ADMINISTRATION**, **Preparation of Solutions**).

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

The chemical name for hydrocortisone sodium succinate 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 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.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

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

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period.

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.

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

INDICATIONS AND USAGE

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, the **intravenous or intramuscular use** of SOLU CORTEF® is indicated as follows:

*Allergic states***:** Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, serum sickness, transfusion reactions, acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), severe psoriasis, severe seborrheic dermatitis.

*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 analogues 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, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

*Gastrointestinal diseases***:** To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis (systemic therapy).

*Hematologic disorders***:** Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), idiopathic thrombocytopenic purpura in adults (intravenous administration only; intramuscular administration is contraindicated), pure red cell aplasia, select cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukemias and lymphomas in adults and acute leukemia of childhood.

Nervous System: Cerebral edema associated with primary or metastatic brain tumor, or craniotomy.

Ophthalmic diseases: Severe acute and chronic allergic and inflammatory processes involving the eye unresponsive to topical corticosteroids, 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.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, aspiration pneumonitis, Loeffler's syndrome not manageable by other means, symptomatic sarcoidosis.

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; synovitis of osteoarthritis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
For the treatment of temporal arteritis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of acute rheumatic carditis; systemic dermatomyositis (polymyositis); systemic lupus erythematosus.

Medical emergencies: SOLU CORTEF® is indicated in the treatment of 1) shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenocortical insufficiency may be present, and 2) 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, etc.) has not been effective.

CONTRAINDICATIONS

SOLU CORTEF® is contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents (see DESCRIPTION).

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

SOLU CORTEF® is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration
Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety

and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General:
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.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).

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

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.

Cardio-renal:
Average and large doses of corticosteroids 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.

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.

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** and **PRECAUTIONS: Drug Interactions, Amphotericin B injection and potassium-depleting agents**).

Endocrine:
Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. 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 reinstituted.

Immunosuppression and Increased Risk of Infection

Corticosteroids, including SOLU-CORTEF, suppress the immune system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic pathogens. Corticosteroids can:

- Reduce resistance to new infections
- Exacerbate existing infections
- Increase the risk of disseminated infections
- Increase the risk of reactivation or exacerbation of latent infections
- Mask some signs of infection

Corticosteroid-associated infections can be mild but can be severe and at times fatal. The rate of infectious complications increases with increasing corticosteroid dosages.

Monitor for the development of infection and consider SOLU-CORTEF withdrawal or dosage reduction as needed. Do not administer SOLU-CORTEF by an intraarticular, intrabursal, or intratendinous route in the presence of acute local infection.

Tuberculosis
If SOLU-CORTEF is used to treat a condition in patients with latent tuberculosis or tuberculin reactivity, reactivation of the disease may occur. Closely monitor such patients for reactivation. .During prolonged SOLU-CORTEF therapy, patients with latent tuberculosis or tuberculin reactivity should receive chemoprophylaxis.

Varicella Zoster and Measles Viral Infections
Varicella and measles can have a serious or even fatal course in non-immune patients taking corticosteroids. In corticosteroid-treated patients who have not had these diseases or are nonimmune,
particular care should be taken to avoid exposure to varicella and measles:
• If a SOLU-CORTEF-treated patient is exposed to varicella, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If varicella develops, treatment with antiviral agents may be considered.
• If a SOLU-CORTEF-treated patient is exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated.

Hepatitis B Virus Reactivation
Hepatitis B virus reactivation can occur in patients who are hepatitis B carriers treated with immunosuppressive dosages of corticosteroids, including SOLU-CORTEF. Reactivation can also occur infrequently in corticosteroid-treated patients who appear to have resolved hepatitis B infection.

Screen patients for hepatitis B infection before initiating immunosuppressive (e.g., prolonged) treatment with SOLU-CORTEF. For patients who show evidence of hepatitis B infection, recommend consultation with physicians with expertise in

managing hepatitis B regarding monitoring and consideration for hepatitis B antiviral therapy.

Fungal Infections
Corticosteroids, including SOLU-CORTEF, may exacerbate systemic fungal infections; therefore, avoid SOLU-CORTEF use in the presence of such infections unless SOLU-CORTEF is needed to control drug reactions. For patients on chronic SOLU-CORTEF therapy who develop systemic fungal infections, SOLU-CORTEF withdrawal or dosage reduction is recommended.

Amebiasis
Corticosteroids, including SOLU-CORTEF, may activate latent amebiasis. Therefore, it is recommended that latent amebiasis or active amebiasis be ruled out before initiating SOLU-CORTEF in patients who have spent time in the tropics or patients with unexplained diarrhea.

Strongyloides Infestation
Corticosteroids, including SOLU-CORTEF, 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.

Cerebral Malaria
Avoid corticosteroids, including SOLU-CORTEF, in patients with cerebral malaria.

Vaccination:
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.
Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison's disease).

Neurologic:
Reports of severe medical events have been associated with the intrathecal route of administration (see **ADVERSE REACTIONS**, Neurologic/Psychiatric).

Ophthalmic:
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 bacteria, fungi, or viruses. The use of oral 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.

Kaposi's Sarcoma:
Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement of Kaposi's sarcoma.

PRECAUTIONS

General:
The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

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.

Cardio-renal:
As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine:
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 reinstituted. 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.

Gastrointestinal:
Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.
There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal:
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 the 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. Special consideration should be given to patients

at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Local injection of a steroid into a previously infected site is not usually recommended.

Neurologic-psychiatric:
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. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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.

Ophthalmic:
Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Other:
Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. In patients with suspected pheochromocytoma, consider the risk of pheochromocytoma crisis prior to administering corticosteroids.

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

Information for Patients:
Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on 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.

Drug Interactions:
Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see **PRECAUTIONS**: **Drug Interactions**, Hepatic Enzyme Inhibitors).

Anticholinesterases: 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.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs that induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin): Drugs that inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: 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.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS**: **Immunosuppression and Increased Risk of Infection Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Corticosteroids have been shown to impair fertility in male rats.

Pregnancy: Teratogenic Effects:

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers:

Systemically administered corticosteroids appear in human milk and could suppress 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 decision should be made whether to continue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age) and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients 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. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). 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. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

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

Geriatric Use:
Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

ADVERSE REACTIONS

The following adverse reactions have been reported with SOLU CORTEF® or other corticosteroids:

Allergic reactions: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Blood and lymphatic system disorders: Leukocytosis.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, burning or tingling (especially in the perineal area, after intravenous injection), cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS**: **Neurologic**), epidural lipomatosis.

Ophthalmic: Central serous chorioretinopathy, exophthalmoses, glaucoma, increased

intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see WARNINGS), malaise, moon face, weight gain.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

OVERDOSAGE

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 the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

Because of possible physical incompatibilities, SOLU CORTEF® should not be diluted or mixed with other solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
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® intravenously over a period of 30 seconds (e.g., 100 mg) 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. 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® is 100 mg to 500 mg, depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

This dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient's

response and clinical condition.

It Should Be Emphasized that Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, 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. Situations that may make dosage adjustments necessary 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 not directly related to the disease entity under treatment. 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. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In pediatric patients, the initial dose of hydrocortisone may vary depending on the specific disease entity being treated. The range of initial doses is 0.56 to 8 mg/kg/day in three or four divided doses (20 to 240 mg/m^2bsa/day). For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

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).

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

HOW SUPPLIED

100 mg Plain Vial.

SOLU CORTEF® 100mg is available in packs containing 1 or 25 vials.

Not all pack sizes may be marketed.

SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

STORAGE CONDITIONS

Store below 25°C.
Use solution only if it is clear.
The solution should be used immediately after reconstitution.

LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya 4672509.

LICENSE NUMBER

062-03-22187

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