**SOLU-CORTEF**

## Table of Content

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## 1. NAME OF THE MEDICINAL PRODUCT

SOLU-CORTEF™ For Injection 100 mg/vial.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydrocortisone sodium succinate equivalent to hydrocortisone 100 mg.

## 3. PHARMACEUTICAL FORM

White, lyophilized powder for solution for injection.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**1. Endocrine Disorders**

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogues 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)
Pre-operatively, 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
Non-suppurative 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:
Post-traumatic osteoarthritis
Synovitis of osteoarthritis
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
Epicondylitis
Acute non-specific tenosynovitis
Acute gouty arthritis
Psoriatic arthritis
Ankylosing spondylitis
Acute and subacute bursitis

Collagen Diseases - During an exacerbation or as maintenance therapy in selected cases of:
Systemic lupus erythematosus

Systemic dermatomyositis (polymyositis)
Acute rheumatic carditis

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

Allergic States - Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
Serum sickness
Bronchial asthma
Drug hypersensitivity reactions
Contact dermatitis
Atopic dermatitis
Urticarial transfusion reactions
Acute non-infectious laryngeal edema (epinephrine is the drug of first choice)

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

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

Hematologic Disorders
Idiopathic thrombocytopenic purpura in adults (I.V. only; I.M. administration is contraindicated)
Secondary thrombocytopenia in adults
Acquired (autoimmune) hemolytic anemia
Erythroblastopenia (RBC anemia)
Congenital (erythroid) hypoplastic anemia

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

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

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

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 section 4.4 Special warnings and precautions for use).

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

**4.2 Posology and method of administration**

This preparation may be administered by intravenous injection, by intravenous 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).

Dosage requirements are variable and must be individualized on the basis of the disease under treatment, its severity and the response of the patient over the entire duration of treatment. A risk/benefit decision must be made in each individual case on an ongoing basis.

The lowest possible dose of corticosteroid should be used to control the condition under treatment for the minimum period. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached.

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 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.

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see section 4.4 Special warnings and precautions for use).

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, the maximum dose being 15 mg/kg.

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 Vial - 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).

## 4.3 Contraindications

Hydrocortisone sodium succinate is contraindicated:

- in patients who have systemic fungal infections.
- in patients with known hypersensitivity to the drug or any component of the formulation.
- for use by the intrathecal route of administration, except as part of certain chemotherapeutic regimens (diluents containing benzyl alcohol must not be used).
- for use by the epidural route of administration.

Administration of live or live-attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

## 4.4 Special warnings and precautions for use

**Immunosuppressant Effects/Increased Susceptibility to Infections**
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.

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.

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 non-immunosuppressive doses of corticosteroids.

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.

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

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

**Immune System Effects**
Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/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.

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

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.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

Drug-induced secondary adrenocortical insufficiency may therefore 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.

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.

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

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

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

**Psychiatric Effects**
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. 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.

**Nervous System Effects**
Corticosteroids should be used with caution in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (also see myopathy statement in Musculoskeletal Effects section).

Severe medical events have been reported in association with the intrathecal/epidural routes of administration.

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

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

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

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

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

**Cardiac Effects**
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.

Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

**Vascular Effects**
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.

Steroids should be used with caution in patients with hypertension.

**Gastrointestinal Effects**
High doses of corticosteroids may produce acute pancreatitis.

Glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain. 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), the risk of developing gastrointestinal ulcers is increased.

Corticosteroids should be used with caution in non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections, also in diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

**Hepatobiliary Effects**
Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring 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.

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.

**Musculoskeletal Effects**
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 anticholinergics, such as 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.

Osteoporosis is generally associated with long-term use and large doses of glucocorticoids. Corticosteroids should be used with caution in patients with osteoporosis.

**Renal and Urinary Disorders**
Corticosteroids should be used with caution in patients with renal insufficiency.

**Investigations**
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.

**Injury, Poisoning and Procedural Complications**
Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury; a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo.

**Other**
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 as to whether daily or intermittent therapy should be used.

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

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

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.

**Use in Children**
Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

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.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Hydrocortisone is metabolized by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and the cytochrome P450 (CYP) 3A4 enzyme. The CYP3A4 enzyme catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS - May decrease hepatic clearance and increase the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, and grapefruit juice), 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 (e.g., rifampin, carbamazepine, phenobarbital, and phenytoin), 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 co-administration.

NON-CYP3A4-MEDIATED EFFECTS - Other interactions and effects that occur with hydrocortisone are described in Table 1 below.

Table 1 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with hydrocortisone.

**Table 1. Important drug or substance interactions/effects with hydrocortisone**

| **Drug Class or Type - DRUG or SUBSTANCE** | **Interaction/Effect** |
|---|---|
| Antibacterial<br>- ISONIAZID | CYP3A4 INHIBITOR |
| Antibiotic, Antitubercular<br>- RIFAMPIN | CYP3A4 INDUCER |
| 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<br>- CARBAMAZEPINE | CYP3A4 INDUCER (and SUBSTRATE) |
| Anticonvulsants<br>- PHENOBARBITAL<br>- PHENYTOIN | CYP3A4 INDUCERS |
| Anticholinergics<br>- NEUROMUSCULAR BLOCKERS | Corticosteroids may influence the effect of anticholinergics.<br>1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see section 4.4 Special warnings and precautions for use, Musculoskeletal Effects, for additional information).<br>2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers. |
| Anticholinesterases | Steroids may reduce the effects of anticholinesterases in myasthenia gravis. |
| Antidiabetics | Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required. |
| Antiemetic<br>- APREPITANT<br>- FOSAPREPITANT | CYP3A4 INHIBITORS (and SUBSTRATES) |

| Drug Class or Type<br>- DRUG or SUBSTANCE | Interaction/Effect |
|---|---|
| Antifungals<br>- ITRACONAZOLE<br>- KETOCONAZOLE | CYP3A4 INHIBITORS (and SUBSTRATES) |
| Antivirals<br>- HIV-PROTEASE INHIBITORS | CYP3A4 INHIBITORS (and SUBSTRATES)<br>1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.<br>2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations. |
| Aromatase Inhibitors<br>- AMINOGLUTETHIMIDE | Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment. |
| Calcium Channel Blocker<br>- DILTIAZEM | CYP3A4 INHIBITOR (and SUBSTRATE) |
| Cardiac Glycosides<br>- 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. |
| Estrogens (including oral contraceptives containing estrogens) | CYP3A4 INHIBITOR (and SUBSTRATE)<br>Estrogens may potentiate effects of hydrocortisone by increasing the concentration of transcortin and thus decreasing the amount of hydrocortisone available to be metabolized. Dosage adjustments of hydrocortisone may be required if estrogens are added to or withdrawn from a stable dosage regimen. |
| - GRAPEFRUIT JUICE | CYP3A4 INHIBITOR |
| Immunosuppressant<br>- CYCLOSPORINE | CYP3A4 INHIBITOR (and SUBSTRATE)<br>Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use. |
| Immunosuppressant<br>- CYCLOPHOSPHAMIDE<br>- TACROLIMUS | CYP3A4 SUBSTRATES |
| Macrolide Antibacterial<br>- CLARITHROMYCIN<br>- ERYTHROMYCIN | CYP3A4 INHIBITORS (and SUBSTRATES) |
| Macrolide Antibacterial<br>- TROLEANDOMYCIN | CYP3A4 INHIBITOR |
| NSAIDs<br>- high-dose ASPIRIN (acetylsalicylic acid) | 1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs.<br>2) Corticosteroids may increase the clearance of high-dose aspirin, 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. |
| Potassium Depleting Agents | When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure. |

## 4.6 Fertility, pregnancy and lactation

### Fertility

Corticosteroids have been shown to impair fertility in animal studies (see section 5.3 Preclinical safety data).

**Pregnancy**
Some animal studies have shown that corticosteroids, including hydrocortisone, when administered to the mother at high doses, may cause fetal malformations. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women. Since adequate human reproductive studies have not been done with hydrocortisone sodium succinate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Some corticosteroids readily cross the placenta. Some retrospective studies have found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses. 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.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

**Lactation**
Corticosteroids are excreted in breast milk.

This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

## 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.*

| **Adverse reactions table** | |
|---|---|
| **System Organ Class** | **Adverse Drug Reactions** |
| ***Infections and infestations*** | Opportunistic infection;<br>Infection |
| ***Neoplasms benign, malignant and unspecified (including cysts and polyps)*** | Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy) |
| ***Blood and lymphatic system disorders*** | Leukocytosis |
| ***Immune system disorders*** | Drug hypersensitivity;<br>Anaphylactic reaction;<br>Anaphylactoid reaction |
| ***Endocrine disorders*** | Cushingoid;<br>Hypothalamic-pituitary-adrenal axis suppression;<br>Steroid withdrawal syndrome |

| Adverse reactions table | |
|---|---|
| **System Organ Class** | **Adverse Drug Reactions** |
| ***Metabolism and nutrition disorders*** | Metabolic acidosis;<br>Sodium retention;<br>Fluid retention;<br>Alkalosis hypokalaemic;<br>Dyslipidaemia;<br>Glucose tolerance impaired;<br>Increased insulin requirement (or oral hypoglycemic agents in diabetics);<br>Lipomatosis;<br>Increased appetite (which may result in Weight increased) |
| ***Psychiatric disorders*** | Affective disorder (including Depression, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation);<br>Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia);<br>Mental disorder;<br>Personality change;<br>Confusional state;<br>Anxiety;<br>Mood swings;<br>Abnormal behaviour;<br>Insomnia;<br>Irritability |
| ***Nervous system disorders*** | Epidural lipomatosis;<br>Intracranial pressure increased;<br>Benign intracranial hypertension;<br>Seizure;<br>Amnesia;<br>Cognitive disorder;<br>Dizziness;<br>Headache |
| ***Eye disorders*** | Central serous chorioretinopathy;<br>Cataract;<br>Glaucoma;<br>Exophthalmos;<br>Vision, blurred (see also section 4.4 Special warnings and precautions for use) |
| ***Ear and labyrinth disorders*** | Vertigo |
| ***Cardiac disorders*** | Cardiac failure congestive (in susceptible patients);<br>Hypertrophic cardiomyopathy (in prematurely born infant) |
| ***Vascular disorders*** | Thrombosis;<br>Hypertension;<br>Hypotension |
| ***Respiratory, thoracic and mediastinal disorders*** | Pulmonary embolism;<br>Gasping syndrome;<br>Hiccups |
| ***Gastrointestinal disorders*** | Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage);<br>Intestinal perforation;<br>Gastric haemorrhage;<br>Pancreatitis;<br>Oesophagitis;<br>Abdominal distension;<br>Abdominal pain;<br>Diarrhoea;<br>Dyspepsia;<br>Nausea |

| Adverse reactions table | |
|---|---|
| **System Organ Class** | **Adverse Drug Reactions** |
| ***Skin and subcutaneous tissue disorders*** | Angioedema;<br>Hirsutism;<br>Petechiae;<br>Ecchymosis;<br>Skin atrophy;<br>Erythema;<br>Hyperhidrosis;<br>Skin striae;<br>Rash;<br>Pruritus;<br>Urticaria;<br>Acne;<br>Skin hypopigmentation |
| ***Musculoskeletal and connective tissue disorders*** | Muscular weakness;<br>Myalgia;<br>Myopathy;<br>Muscle atrophy;<br>Osteoporosis;<br>Osteonecrosis;<br>Pathological fracture;<br>Neuropathic arthropathy;<br>Arthralgia;<br>Growth retardation |
| ***Reproductive system and breast disorders*** | Menstruation irregular |
| ***General disorders and administration site conditions*** | Impaired healing;<br>Oedema peripheral;<br>Fatigue;<br>Malaise;<br>Injection site reaction |
| ***Investigations*** | Intraocular pressure increased;<br>Carbohydrate tolerance decreased;<br>Blood potassium decreased;<br>Urine calcium increased;<br>Alanine aminotransferase increased;<br>Aspartate aminotransferase increased;<br>Blood alkaline phosphatase increased;<br>Blood urea increased;<br>Suppression of reactions to skin tests* |
| ***Injury, poisoning and procedural complications*** | Spinal compression fracture;<br>Tendon rupture |

* Not a MedDRA PT

## 4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

Hydrocortisone is dialyzable.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

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.

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

The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, 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.

## 5.2 Pharmacokinetic properties

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 2.

**Table 2. 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 2). 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 (i.e., cortisol) is metabolized by 11β-HSD2 to cortisone, and further to dihydrocortisone and tetrahydrocortisone. Other metabolites include dihydrocortisol, 5α-dihydrocortisol, tetrahydrocortisol, and 5α-tetrahydrocortisol. Cortisone can be converted to cortisol through 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).

Hydrocortisone is also metabolized by CYP3A4 to 6β-hydroxycortisol (6β-OHF), and 6β-OHF varied from 2.8% to 31.7% of the total metabolites produced, demonstrating large inter-individual variability.

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.

**5.3 Preclinical safety data**

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

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*. However, the biological relevance of these findings is not clear since hydrocortisone did not increase tumor incidences in male and female rats during a 2-year carcinogenicity study. Fludrocortisone (9α-fluorohydrocortisone, structurally similar to hydrocortisone) was negative in the human lymphocyte chromosome aberration assay.

Reproductive 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.

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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium biphosphate, sodium phosphate.

### 6.2 Incompatibilities

None stated.

### 6.3 Shelf-life

Please refer to expiry date of outer carton.

### 6.4 Special precautions for storage

Store unreconstituted product below 30°C.

Refer to Section 4.2 Posology and method of administration. Store solution below 25°C and protect from light. Use solution only if it is clear. Unused solution should be discarded after 3 days.

### 6.5 Nature and contents of container

2 mL hydrolytic Type 1 glass vial closed with butyl rubber stopper.

### 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

## 7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017, USA

Solu-Cortef-SIN-0123/0
Date of last revision: January 2023

**Package leaflet: Information for the patient**
**SOLU-CORTEF FOR INJECTION 100 mg/vial**
hydrocortisone sodium succinate

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions please ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What SOLU-CORTEF is and what it is used for

SOLU-CORTEF contains hydrocortisone sodium succinate. Hydrocortisone belongs to a group of medicines called corticosteroids or steroids. Corticosteroids are produced naturally in your body and are important for many body functions.

Boosting your body with extra corticosteroid such as SOLU-CORTEF can help when injected by a doctor or nurse if your body cannot produce enough corticosteroid due to problems with your **adrenal glands** (e.g., adrenal insufficiency).

Corticosteroids can also help treat non-hormonal disorders. These include inflammatory or allergic conditions affecting the joints, skin, eye, lungs, blood and gut.

SOLU-CORTEF may be prescribed to treat conditions other than those listed above, such as adrenal insufficiency and other medical emergencies like treatment of shock associated with this.

You must talk to a doctor if you do not feel better or if you feel worse or are unsure why you have been given this medicine.

## 2. What you need to know before you are given SOLU-CORTEF

**Do not use SOLU-CORTEF:**

- If you think you have ever suffered an **allergic reaction**, or any other type of reaction after being given SOLU-CORTEF, or any other medicine containing a corticosteroid, or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may cause a skin rash or reddening, swollen face or lips or shortness of breath.

- If you have a widespread **fungal infection**.
- If you have recently had, or are about to have any 'live' vaccination.

**See your doctor immediately if you have any of the above.**

**Warnings and precautions**

Talk to your doctor or nurse before taking this medicine if you have any of the following conditions.

Your doctor may also have to monitor your treatment more closely, alter your dose or give you another medicine.

- **Chickenpox, measles** or a **herpes** eye infection. If you think you have been in contact with someone with chickenpox or measles and you have not already had these illnesses, or if you are unsure if you have had them.
- **Tuberculosis** (TB).
- **Kaposi's sarcoma** (a type of cancer).
- Septic shock (a dangerous drop in blood pressure caused by severe infection).
- If you have history of allergy to any drug.
- If you are under unusual **stress**.
- If you develop **adrenal insufficiency**.
- **Cushing's disease** (a hormone disorder caused by high levels of cortisol in the blood).
- **Hypothyroidism** (an under-active thyroid).
- **Diabetes**.
- Severe **depression**. This includes having had depression before while taking steroid medicines like SOLU-CORTEF.
- **Fits or seizure**.
- **Myasthenia gravis** (a condition causing tired and weak muscles).
- **Glaucoma** (increased pressure in the eye).
- **Cataract** (clouding of the lens).
- You have recently suffered a **heart attack**.
- **Heart problems**, including heart failure.
- If you have **thromboembolic disorders** (disorders due to formation of blood clots).
- **Hypertension** (high blood pressure).
- If you develop **pancreatitis** (inflammation of the pancreas which causes severe pain in the abdomen and back).
- **Peritonitis** (inflammation of the thin lining (peritoneum) around the gut and stomach).
- **Stomach ulcer, diverticulitis** (inflammation of the bowel wall) or other serious stomach or intestinal problems.
- **Kidney** or **liver** disease.
- **Muscle problems** (pain or weakness) have happened while taking steroid medicines in the past.
- **Osteoporosis** (brittle bones).
- **Fluid retention in the body**.
- You are suffering from a **traumatic brain injury**.

- **Pheochromocytoma** (a rare tumour of adrenal gland tissue. The adrenal glands are located above the kidneys).
- **Tumour lysis syndrome** (a life-threatening emergency that occurs because of the rapid breakdown of multiplying cancer cells causing high levels of calcium, uric acid, potassium and phosphate) in patients with cancer.

Tell your doctor if you suspect an infection has occurred, as corticosteroids can make infections more likely and may mask their signs.

This medicine is not recommended for injection via the spinal cord (intrathecal or epidural). Serious side effects have been reported with this use on occasions.

Long term therapy of corticosteroids in high doses can cause an abnormal amount of fat deposition on or outside the lining of the spine (epidural lipomatosis).

Caution should be exercised with corticosteroids as they can cause an eye condition (central serous chorioretinopathy) where a collection of fluid forms under the light-sensitive layer of tissue at the back of the inner eye (retina) causing visual impairment and may lead to retinal detachment.

If hydrocortisone is given to a prematurely born baby, monitoring of heart function and structure may be needed.

**Other medicines and SOLU-CORTEF**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should tell your doctor if you are taking any of the following medicines which can affect the way SOLU-CORTEF or the other medicine works:

- **Isoniazid** - used to treat bacterial infections.
- **Rifampin** - antibiotics used to treat tuberculosis (TB).
- **Anticoagulants** - used to 'thin' the blood.
- **Carbamazepine, phenobarbital** and **phenytoin** - used to treat epilepsy.
- **Anticholinergics** (such as **Pancuronium** and **Vecuronium**) - medicines called neuromuscular blocking agents which are used in some surgical procedures.
- **Anticholinesterase**s - used to treat myasthenia gravis (a muscle condition).
- **Antidiabetics** - medicines used to treat high blood sugar.
- **Antiemetic** (such as **Aprepitant** and **Fosaprepitant) -** used to prevent nausea and vomiting resulting from cancer treatment.
- **Itraconazole** or **ketoconazole** – used to treat fungal infections.
- **Antivirals** (such as ritonavir, indinavir) - used to treat HIV infections.
- **Diltiazem** - used for heart problems or high blood pressure.
- **Digoxin** - used for heart failure and/or an irregular heart beat.
- **Estrogens containing products -** including oral contraceptives.
- **Cyclosporine** - used to treat conditions such as severe rheumatoid arthritis, severe psoriasis or following an organ or bone marrow transplant.

- **Cyclophosphamide** and **tacrolimus** - used following an organ transplant to prevent rejection of the organ and for treatment of autoimmune diseases.
- **Antibiotics** (such as erythromycin, clarithromycin, troleandomycin).
- **Aspirin** and non-steroidal anti-inflammatory medicines (also called **NSAIDs**) used to treat mild to moderate pain.
- Potassium depleting agents – **Diuretics** (sometimes called water tablets), **amphotericin B, xanthines or beta$_2$ agonists** (e.g., medicines used to treat asthma).
- **Vaccines** - tell your doctor or nurse if you have recently had, or are about to have any vaccination. You **should not** have 'live' vaccines while using this medicine. Other vaccines may be less effective.
- **Grapefruit juice**.

**If you are taking long term medication(s)**
If you are being treated for diabetes, high blood pressure or water retention (oedema) tell your doctor as he/she may need to adjust the dose of the medicines used to treat these conditions.

**Before you have any operation** tell your doctor, dentist or anesthetist that you are taking this medicine.

**If you require a test to be carried out by your doctor or in hospital** it is important that you tell the doctor or nurse that you are taking SOLU-CORTEF. This medicine can affect the results of some tests.

**Pregnancy and breast-feeding**

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Corticosteroids can cross the placenta which is a risk associated with low birth weight of the baby.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Tell your doctor if you are breast feeding as corticosteroid medicines may get into breast milk.

**Driving and using machines**

The effect of this class of medicines on the ability to drive or use machinery has not been studied. There are undesirable effects observed with the use of this medicine such as syncope (fainting), vertigo (sensation of rotation or movement of oneself or the surrounding), and convulsions (seizures). If you are affected by any of them, you should not drive or operate machinery.

## 3. How SOLU-CORTEF is given to you

You should inform **anyone** who gives you treatment (such as a doctor, nurse or dentist) while you are taking this medicine.

If you are admitted to hospital for any reason always tell your doctor or nurse that you are taking this medicine.

**Dosage information**

Your doctor will decide on the site of injection, how much of the medicine and how many injections you will receive depending on the condition being treated and its severity. Your doctor will inject you with the lowest dose for the shortest possible time to get effective relief of your symptoms.

**Adults**

SOLU-CORTEF will be given as an injection by your doctor or nurse, either into a vein (intravenous) or into a muscle (intramuscular). Usually the first dose is given into a vein, especially in an emergency.

It will be given slowly over a period of between 30 seconds (e.g., doses equivalent to 100 mg hydrocortisone) to 10 minutes (e.g., 500 mg hydrocortisone or more). Depending on your condition a repeat dose may be injected at intervals of between 2 to 6 hours. Large doses should normally be used for only two to three days.

For intravenous or intramuscular injection, the medicine is first dissolved in sterile water for injection or sterile sodium chloride. If the medicine is to be given by infusion (using a pump or drip) it is first dissolved in sterile water for injection then mixed with another suitable fluid. No other medicines should be mixed with it.

**Use in children and adolescents**

Corticosteroids can affect growth in children so your doctor will prescribe the lowest dose (should not be less than 25 mg a day) that will be effective for your child. Maximum dose is 15 mg/kg.

**If you are given more SOLU-CORTEF than you should have**

If you think you have been given too many injections of this medicine please speak to your doctor immediately.

**Stopping/reducing the dose of your SOLU-CORTEF**

Your doctor will decide when it is time to stop your treatment.

You will need to come off this treatment slowly if you have been given SOLU-CORTEF for long duration.

You will need to come off this medicine slowly to avoid **withdrawal symptoms**. Some of these symptoms may include peeling skin, fever, muscle and joint pains, and weight loss.

If your symptoms seem to return or get worse as your dose of this medicine is reduced tell your doctor immediately.

**Mental problems while taking SOLU-CORTEF**

Mental health problems can happen while taking steroids like SOLU-CORTEF (see also section 4, **Possible side effects**).

- These illnesses can be serious.
- Usually they start within a few days or weeks of starting the medicine.
- Most of these problems go away if the dose is lowered or the medicine is stopped. However if the problems do happen they might need treatment.

Talk to a doctor if you (or someone using this medicine) show any signs of mental problems. This is particularly important if you are depressed, or might be thinking about suicide. In a few cases psychological symptoms have happened when doses are being lowered or stopped.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will have given you this medicine for a condition which if not treated properly could become serious.

**In certain medical conditions, medicines like SOLU-CORTEF (steroids) should not be stopped abruptly. If you suffer from any of the following symptoms seek IMMEDIATE medical attention. Your doctor will then decide whether you should continue taking your medicine:**

- **Allergic reactions,** such as skin rash, swelling of the face or wheezing and difficulty breathing. This type of side effect is rare, but can be serious.
- **Acute pancreatitis**, stomach pain which may spread through to your back, possibly accompanied by vomiting, shock and loss of consciousness.
- **Ulcers or bleeding ulcers,** symptoms of which are severe stomach pain which may go through to the back and could be associated with bleeding from the back passage, black or bloodstained stools and/or vomiting blood.
- **Infections.** This medicine can hide or change the signs and symptoms of some infections, or reduce your resistance to the infection, so that they are hard to diagnose at an early stage. Symptoms might include a raised temperature and feeling unwell. Symptoms of a flare up of a previous TB infection could be coughing up blood or pain in the chest. This medicine may also make you more likely to develop a severe infection.
- **Pulmonary embolus** (blood clot in the lung**)** symptoms include sudden sharp chest pain, breathlessness and coughing up blood.
- **Raised pressure within the skull** of children, symptoms of which are headaches with vomiting, lack of energy and drowsiness.

**If you experience any of the following side effects, or notice any other unusual effects not mentioned in this leaflet, tell your doctor straight away.**

**Blood, heart and circulation**

- High blood pressure, symptoms of which are headaches, or generally feeling unwell.
- Problems with the pumping of your heart (heart failure) symptoms of which are swollen ankles, difficulty in breathing and palpitations (awareness of heart beat) or irregular beating of the heart, irregular or very fast or slow pulse.
- Increased numbers of white blood cells (leukocytosis).
- Low blood pressure symptoms may include dizziness, fainting, lightheadedness, blurred vision, a rapid, or irregular heartbeat (palpitations), general weakness.

**Body water and salts**

- Swelling and high blood pressure, caused by increased levels of water and salt content.
- Cramps and spasms, due to the loss of potassium from your body. In rare cases this can lead to congestive heart failure (when the heart cannot pump properly).

**Digestive system**

- Nausea (feeling sick) or vomiting (being sick).
- Ulcers.
- Indigestion.
- Bloated stomach.
- Abdominal pain.
- Diarrhoea.
- Hiccups.
- Bleeding.

**Ears**

- A feeling of dizziness or spinning (vertigo).

**Eyes**

- Glaucoma (raised pressure within the eye, causing pain in the eyes and headaches).
- Cataracts (indicated by failing eyesight).
- Protruding of the eyeballs (exophthalmos).
- Blurred or double vision.
- Eye condition (central serous chorioretinopathy) where a collection of fluid forms under the light-sensitive layer of tissue at the back of the inner eye (retina) causing visual impairment and may lead to retinal detachment.

**General disorders**

- Poor wound healing.
- Feeling tired or unwell.
- Skin reactions at the site of injection.
- Water retention in the extremities.

**Hormones and metabolic system**

- Slowing of normal growth in infants, children and adolescents which may be permanent.
- Irregular or no periods in women.
- Round or moon-shaped face (Cushingoid facies).

- Increased appetite and weight gain.
- Prolonged therapy can lead to lower levels of some hormones which in turn can cause low blood pressure and dizziness. This effect may persist for months.
- Blood urea increased.
- The amount of certain chemicals (enzymes) called alanine transaminase, aspartate transaminase and alkaline phosphatase that help the body digest drugs and other substances in your body may be raised after treatment with a corticosteroid.
- Elevation of lipid levels e.g., cholesterol level in the blood.
- Abnormal fat deposition in the body.
- Diminished sex drive.
- Difficulty sleeping.

**Immune system**
- Increased susceptibility to infections.
- Suppression of reactions to skin tests.
- Sensitivity to cold.
- Unexplained allergies.

**Muscles and bones**
- Muscle weakness or wasting.
- Brittle bones (bones that break easily).
- Broken bones or fractures.
- Breakdown of bone and joint due to poor circulation of blood, this causes pain in the hip.
- Torn muscle tendons causing pain and/or swelling.

**Nerves and mood issues**
Steroids, including SOLU-CORTEF, can cause serious mental health problems.
- Feeling depressed, including thinking about suicide.
- Feeling high (mania) or moods that go up and down.
- Feeling anxious, having problems sleeping or being confused and losing your memory.
- Feeling, seeing or hearing things which do not exist. Personality change.
- Other nervous system side effects may include seizures, dizziness, difficulty breathing, irritability.
- Headache.

**Skin**
- Acne.
- Thinning of skin.
- Stretch marks (skin striae).
- Bruising.
- Small purple/red patches on the skin.
- Pale patches on your skin, or raised patches which are an unusual colour.
- Excessive growth of bodily and facial hair.
- Rash, itching, hives.
- Increased sweating.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store SOLU-CORTEF

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
This medicine must be stored below 30°C.
Once the medicine has been mixed with the recommended diluent the solution should be stored below 25°C and protect from light. Unused solution should be discarded after 3 days.

Your doctor will check that the solution contains no particles and is not discolored before using it.

## 6. Contents of the pack and other information

**What SOLU-CORTEF contains**
The active substance is hydrocortisone sodium succinate (equivalent to 100 mg hydrocortisone).
The other ingredients are sodium biphosphate and sodium phosphate.

**What SOLU-CORTEF looks like and contents of the pack**
SOLU-CORTEF is a white, lyophilized powder in a clear glass vial fitted with a rubber cap.

Solu-Cortef-SIN-0123/PIL/1
Date of last revision: September 2023