SOLU-CORTEF

Hydrocortisone sodium succinate

100 mg Powder and solvent for solution for injection
250 mg Powder and solvent for solution for injection

Reference market: Belgium

AfME markets using the same label: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solu-Cortef 100 mg Powder and solvent for solution for injection
Solu-Cortef 250 mg Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance of Solu-Cortef is hydrocortisone.
This is present in the form of hydrocortisone sodium succinate (133.67 mg and 334.18 mg), respectively equivalent to 100 mg and 250 mg of hydrocortisone.

Excipient with known effect:
Solu-Cortef 250 mg Powder and solvent for solution for injection contains 25.3 mg sodium per Act-O-Vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Solu-Cortef contains lyophilized hydrocortisone sodium succinate for intravenous and intramuscular administration. This highly concentrated aqueous solution will rapidly elevate the blood level.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glucocorticoids should only be considered as a purely symptomatic treatment, unless in case of some endocrine disorders, where they are used as substitution treatment.
ENDOCRINE DISORDERS
- Primary or secondary adrenocortical insufficiency
- Acute adrenocortical insufficiency

(For these indications, hydrocortisone or cortisone are the medicines of first choice; where applicable, synthetic analogues can be combined with mineral corticoids; supplementation with mineral corticoids is particularly important in children.
- Prior to surgical operations and in the event of serious illness or trauma or, in patients suffering from known adrenocortical insufficiency or in the event of doubtful adrenocortical reserve
- Shock unresponsive to conventional therapy when adrenocortical insufficiency is present or presumed
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcaemia associated with cancer

NON-ENDOCRINE DISORDERS
1. Allergic disorders
   Control of severe or incapacitating allergic conditions not responding to adequate conventional treatments in:
   - Serum sickness
   - Bronchial asthma
   - Drug hypersensitivity reactions
   - Contact dermatitis
   - Atopic dermatitis
   - Urticarial transfusion reactions
   - Quincke’s edema (epinephrine is the drug of first choice)

2. Respiratory disorders

- Symptomatic pulmonary sarcoidosis
- Loeffler's syndrome not responding to standard treatment
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous drugs
- Aspiration pneumonitis

3. Hematologic disorders
   - Idiopathic thrombocytopenica purpura in adults (intravenous administration only; intramuscular administration is contraindicated)
   - Secondary thrombocytopenia in adults
   - Acquired (autoimmune) hemolytic anemia
   - Erythroblastopenia (aplastic anemia)
   - Congenital hypoplastic anemia

4. Neoplastic disorders
   For palliative management of:
   - Leukaemias and lymphomas in adults
   - Acute childhood leukaemia

5. Medical emergencies
   Solu-Cortef is useful in the treatment of:
   - Shock not responding to the standard therapy
   - Acute allergic disorders (status asthmaticus, anaphylactic reactions, insect bites, etc.)

Although there are no well controlled (double-blind with placebo) clinical trials, data from experimental animal models indicate that corticoids may be useful in shock states in which standard therapy (e.g. fluid replacement, etc.) has not been effective. See also section 4.4 "Special warnings and precautions for use".

6. Other disorders
   - Tuberculous meningitis with subarachnoid block or impending block when used concurrently with adequate antituberculous chemotherapy
   - Trichinosis with neurologic or myocardial involvement

4.2 Posology and method of administration

Posology
Intravenous injection is the method of first choice for initial treatment of emergency cases. A longer-acting injectable or oral preparation must be considered after this initial period.

The duration of the intravenous administration depends on the dose; it can vary from 30 seconds (100 mg for example) to 10 minutes (500 mg or more, for example).

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.

Treatment with high doses of corticosteroids may generally be continued only until the patient's condition has stabilized (usually not longer than 48 to 72 hours).

If a treatment with high doses of hydrocortisone needs to be continued for longer than 48 to 72 hours hypernatriaemia can occur. In that case it may be desirable to replace Solu-Cortef by a corticosteroid preparation such as 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).

The initial dose of Solu-Cortef is 100 mg to 500 mg or more, depending on the severity of the condition. This dose may be repeated every 2, 4 or 6 hours if the clinical condition of the patient requires it.

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

Corticosteroid therapy is an adjuvant; it does not replace conventional treatment.

Paediatric population
The dosage of Solu-Cortef in paediatrics is determined more by the seriousness of the disorder and the patient's response than by the patient's age or bodyweight. The doses may be reduced but must never amount to less than 25 mg per day.

Method of administration
Solu-Cortef can be administered in intramuscular or intravenous injection or in intravenous infusion.

4.3 Contraindications

Hydrocortisone sodium succinate is contraindicated:

- In patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- In patients with systemic fungal infections:
- 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 vaccines based on live or live attenuated virus is contra-indicated in patients receiving immunosuppressive doses of corticosteroids.

4.4 Special warnings and precautions for use

Special risk groups:
Patients belonging to the following risk groups should be treated under close medical supervision and for the shortest possible period:

- Children and adolescents: growth retardation can occur in children receiving long-term treatment with glucocorticoids in divided daily doses. Such a regimen is justified only in very severe indications. Growth and development should be closely monitored in infants and children receiving long-term corticosteroid treatment.
- Diabetics: signs of latent diabetes mellitus or increased requirement of insulin or oral hypoglycaemic agents.
- Hypertensive patients: aggravation of arterial hypertension.
- Patients with osteoporosis.
- Patients with active or latent peptic ulcer, diverticulitis, recent intestinal anastomoses, non-specific ulcerative colitis if there is a risk of perforation and abscess or other pyogenic infections.
- Patients with a predisposition for thromboembolism. Thrombosis, including venous thromboembolism, has been reported with corticosteroids. As a result, corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.
- Patients with myasthenia gravis
- Patients with renal insufficiency
- Patients with a history of psychiatric disease: existing emotional instability and psychotic tendencies may be aggravated by corticosteroids. Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, sullen temper, personality disorders and severe depression to frank psychotic manifestations:

- Patients with some infections such as tuberculosis: in active tuberculosis the use of Solu-Cortef should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used in conjunction with appropriate antituberculous chemotherapy. Patients with latent tuberculosis or tuberculin reactivity should be monitored closely during corticotherapy to detect possible reactivation of the disease. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.
- Patients with some viral conditions such as herpes and shingles with ocular symptoms: glucocorticoids should be used with caution in case of ocular herpes simplex because of the risk of corneal perforation.
- Patients with Epilepsy

Immunosuppressant Effects/Increased Susceptibility to Infections
Glucocorticosteroids may increase susceptibility to infections, may mask some signs of infection, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Systemic infections involving bacteria, viruses, moulds, protozoa or worms, can be associated with corticosteroid treatment, either alone or in combination with other immunosuppressant substances which have an effect on cell immunity, humoral immunity or neutrophil activity. These infections may be of a moderate or severe nature and in some cases fatal. The number of infections rises with increasing corticoid dosage.

Monitor for the development of infection and consider withdrawal of corticosteroids or dosage reduction as needed.

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 being treated with immunosuppressant doses of corticosteroids. Dead or inactivated and biogenetically obtained vaccines may be administered however to these patients. However the response to such vaccines may be diminished or they can even be ineffective. The necessary immunization procedures should be however undertaken in patients being treated with non-immunosuppressant doses of corticosteroids.

The occurrence of Kaposi sarcoma has been reported in patients treated with corticosteroids. Stopping of the corticosteroid therapy can bring about 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 of this product, especially when the patient has a history of allergy to this type of product.

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 adrenal insufficiency). The degree and duration

of adrenal 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.

Patients subject to severe stress after corticosteroid therapy must be kept under close observation for symptoms of adrenocortical insufficiency.

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This 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. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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 glucocorticosteroids on patients with hypothyroidism and in those with cirrhosis. In patients with hyper- or hypothyroidism, thyroid hormone substitution settings should be monitored during corticosteroid therapy.

Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with hydrocortisone-induced hypokalaemia. TPP must be suspected in patients treated with hydrocortisone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism.
If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

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
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.

Cases of epidural lipomatosis have been reported in patients receiving corticosteroids, usually at high doses over the long-term.

Ocular Effects

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 can 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
Steroids should be used with caution in patients with hypertension.

Gastrointestinal Effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, 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.

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.

Musculoskeletal Effects
The occurrence of acute myopathies is reported with the use of high doses of corticosteroids. These occur mostly in patients with neuromuscular transmission disorders (myasthenia gravis for example) or in patients undergoing simultaneous treatment with anticholinergics such as neuromuscular-inhibiting medication (pancuronium, for example).

This acute myopathy can occur anywhere and can affect the eye and respiratory muscles and can result in quadriparesis. An increase in creatine kinase can be induced. Weeks or even years may pass after the corticosteroid therapy has stopped before a clinical improvement or cure takes place.

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

Injection into the deltoid muscle should be avoided because of the high incidence of subcutaneous atrophy.

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

Investigations
Hydrocortisone can lead to increase in blood pressure, water- and salt-retention and increased potassium excretion. A sodium-free diet 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 multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

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 and 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.

The duration of the treatment should in general be kept as short as possible. Medical surveillance is recommended during chronic treatment (see section 4.2). The discontinuation of a chronic treatment should also occur under medical surveillance (gradual discontinuation, evaluation of the adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5).

Concomitant use of oral anticoagulants and hydrocortisone may increase the risk of bleeding. There are reports of diminished effects of oral anticoagulants as well. For patients treated with vitamin K antagonists, more frequent monitoring of prothrombin time (INR) is recommended, especially during treatment initiation or dose adjustments of hydrocortisone (see section 4.5).

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects (see section 4.5).

A crisis of pheochromocytoma, which may be fatal, was reported after the administration of systemic corticosteroids. Corticosteroids may only be administered to patients with suspected or identified pheochromocytoma after an appropriate assessment of benefits/risks.

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.

Possible effects of corticosteroids include adrenal suppression, decrease in bone mineral density, cataract and glaucoma.

Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g. skin tests, thyroid hormone levels). Suppression of reactions to skin tests may occur.

Paediatric population
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. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

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.

Excipients information
Solu-Cortef 100 mg Powder and solvent for solution for injection contains less than 1 mmol sodium (23 mg) per Act-O-Vial, that is to say essentially 'sodium-free'.

Solu-Cortef 250 mg Powder and solvent for solution for injection contains 25.3 mg sodium per Act-O-Vial, equivalent to 1.27% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 coadministration.
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.

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Oral anticoagulants (Vitamin K antagonists and non-vitamin K antagonists)	The effect of the concomitant use of corticosteriods with oral anticoagulants, vitamin K antagonist (e.g., warfarin, acenocoumarol, fluindione) could vary. There are reports of enhanced as well as diminished effects of these anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics	Corticosteroids may influence the effect of anticholinergics.

Drug Class or Type **- DRUG or SUBSTANCE**	**Interaction/Effect**
- NEUROMUSCULAR BLOCKERS	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). 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. Such an interaction can be expected when using any neuromuscular blocker acting by competitive antagonism.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations and dosage adjustments of antidiabetic agents may be required.
Antiemetics - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungals - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase Inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate hormonal changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Cardiac Glycosides - DIGOXIN	Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.
Estrogens (including oral contraceptives containing estrogens)	CYP3A4 INHIBITOR (and SUBSTRATE) 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 - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterials - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs - high-dose ASPIRIN	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs.

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
(acetylsalicylic acid)	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.
Pharmacokinetic enhancer - COBICISTAT	CYP3A4 INHIBITORS
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 agonist receptors. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.
Vaccines	Administration of live or live attenuated vaccines is contraindicated in patients being treated with immunosuppressant doses of corticosteroids. Dead or inactivated vaccines may be administered however to these patients. However the response to such vaccines may be diminished. The necessary immunization procedures may be undertaken in patients being treated with non-immunosuppressant doses of corticosteroids.

4.6 Fertility, pregnancy and lactation

Pregnancy

Some corticosteroids readily cross the placenta. Some retrospective studies revealed an increased incidence in low birth weight in infants whose mothers had received corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

Chronic use of higher doses should be avoided as much as possible because of the risk of adrenal insufficiency in the neonate. Though neonatal adrenal insufficiency is rare in infants who were exposed *in utero* to corticosteroids, infants born of mothers who have received substantial doses of glucocorticoids during pregnancy, should be carefully observed and evaluated for signs of adreal insufficiency.

Cases of cataract have been observed in infants born of mothers treated with long-term corticosteroids during pregnancy.

In case of labour and delivery no effects are known.

Some animal studies have shown that corticosteroids, including hydrocortisone, when administered during pregnancy at high doses, may cause fetal malformations (see section 5.3). However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.

Since safety in pregnancy has not been adequately demonstrated 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 foetus.

Breast-feeding

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.

There is no evidence that corticosteroids are carcinogenic or mutagenic.

Fertility

Animal studies have shown that corticosteroids may impair fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Although visual disorders belong to the rare adverse reactions, caution is recommended by patients driving cars and/or using machines.

4.8 Undesirable effects

Summary of safety profile

The following undesirable effects are typical for systemic corticosteroids.
Hypersensitivity reactions may occur at the beginning of treatment. Serious infections, including opportunistic infections, may also occur with corticosteroid treatment (see section 4.4). Other undesirable effects include: seizures, pathological and vertebral compression fractures, peptic ulcers with perforation or haemorrhage, tendon rupture, psychic and psychotic disorders (see section 4.4), cushingoid disorders, decreased glucose tolerance, increased intraocular pressure, cataract, atrophy of the skin and fluid retention.

Tabulated list of adverse reactions

General side effects may be observed. They rarely occur during treatment of very short duration, but must nonetheless be sought attentively, a precaution common to all corticosteroids and not specific to a particular product. Glucocorticoids can have the following general adverse events:

Side effects	
System Organ Class	**Frequency unknown (cannot be estimated from the available data)**
Infections and infestations	Opportunistic infections; Infection.
Benign, malignant and unspecified tumours (including cysts and polyps)	Kaposi's sarcoma has been reported in patients treated with corticosteroids.
Blood and lymphatic system disorders	Leukocytosis.
Immune system disorders	Drug hypersensitivity; Anaphylactic reactions; Anaphylactoid reaction.
Endocrine disorders	Cushing's syndrome; Hypothalamic pituitary-adrenal axis suppression; Steroid withdrawal syndrome.
Metabolic and nutritional disorders	Metabolic acidosis; Sodium retention; Fluid retention; Alkalosis hypokalemic; Dyslipidaemia; Impaired glucose tolerance; Increased insulin need (or oral hypoglycemic agents in diabetics); Reactivation of latent diabetes mellitus; Lipomatosis; Increased appetite (which may result in weight increased).
Psychiatric disorders	Affective disorder (including Depression, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation); Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behaviour; Insomnia; Irritability.
Nervous system disorders	Epidural lipomatosis; Increased intracranial pressure; Benign intracranial hypertension; Seizures; Amnesia; Cognitive disorder; Dizziness; Headache.
Ocular disorders	Central serous chorioretinopathy; Cataract; Glaucoma; Exophthalmos; Vision, blurred (see section 4.4).
Ear and labyrinth disorders	Vertigo.
Cardiac disorders	Congestive heart failure (in susceptible patients); Hypertrophic cardiomyopathy in prematurely born infants.
Vascular disorders	Thrombosis; Hypertension; Hypotension.
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism; Gasping syndrome (respiratory disorder characterized by a persistent gasping for breath); Hiccups.
Gastrointestinal disorders	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); Intestinal perforation; Gastric

Side effects	
System Organ Class	**Frequency unknown (cannot be estimated from the available data)**
	haemorrhage; Pancreatitis; Oesophagitis; Abdominal distention; Abdominal pain; Diarrhoea; Dyspepsia; Nausea.
Skin and subcutaneous tissue disorders	Angioedema; Hirsutism; Petechiae; Bruising; Atrophy of the skin; Erythema; Hyperhidrosis; Skin striae; Rash; Pruritus; Urticaria; Thin and fragile skin; Facial erythema; Acne; Skin hypopigmentation; Panniculitis*.
Musculoskeletal and connective tissue disorders	Myalgia, Steroidal myopathy; Muscle atrophy; Muscular weakness; Osteonecrosis; Aseptic necrosis; Osteoporosis; Pathological fractures; Neuropathic arthropathy; Arthralgia; Inhibition of growth in children.
Reproductive system and breast disorders	Irregular menstruation.
General disorders and anomalies at the site of administration	Slowed healing of wounds; Oedema peripheral; Fatigue; Malaise; Injection site reaction.
Investigations	Increased intraocular pressure; Decreased glucose tolerance; Decreased serum potassium; Increase calcium excretion; There may be a transient and moderate increase in ALT, ALS and blood alkaline phosphatase, with no apparent clinical syndromes; Weight increased; Blood urea increased.
Lesions, toxicity and procedural complications	Vertebral compression fractures; Tendon rupture.

* Few cases of panniculitis have been reported following dose reduction or discontinuation of therapy, especially after long-term, high-dose treatment. Panniculitis is more common in paediatric patients than in adults, and most cases resolve spontaneously.

The following side effects may be observed in parenteral corticosteroid therapy:
Anaphylactic or allergic reactions with or without circulatory collapse
Cardiac arythmias and cardiac arrest
Bronchospasm
Hypotension or hypertension

Pediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Growth retardation can occur in children receiving long-term treatment with glucocorticoids in divided daily doses (see section 4.4).
Hypertrophic cardiomyopathy in preterm infants (frequency not known) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

To Report side effects

- **Saudi Arabia**

National Pharmacovigilance Centre (NPC)
- SFDA Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

- **Other GCC States**

- Please contact the relevant competent authority.

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. Chronic overdosage induces typical Cushing symptoms. Hydrocortisone is dialyzable.

In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

The therapeutic activity of Solu-Cortef is qualitatively identical to that of hydrocortisone.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticoids, ATC code: H02AB09

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-water-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 persist for a variable period.

The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by depression of polynuclear eosinophil count, following intravenous administration, is five to one. This is consistent with the relative oral potency of methylprednisolone and hydrocortisone.

Glucocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin), and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the numerous effects of glucocorticoids after systemic use. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli. They also act on the cardiovascular system, the skeletal muscles and the central nervous system.

- Effect on the inflammatory and immune process:
  - The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for most of the therapeutic applications. These properties lead to the following results:
  - reduction of the immunoactive cells near the inflammation focus;
  - reduced vasodilation;
  - stabilization of the lysosomal membranes;
  - inhibition of phagocytosis;
  - reduced production of prostaglandines and related substances.
- Effect on carbohydrate and protein metabolism:
  - Glucocorticoids have a protein catabolic action. The liberated amino acids are converted into glucose and glycogen in the liver by means of the gluconeogenesis process. Glucose absorption in peripheral tissues decreases, which leads to hyperglycemia and glucosuria, especially in patients who are prone to diabetes.
- Effect on lipid metabolism:
  - Glucocorticoids have a lipolytic action. This lipolytic activity mainly affects the limbs. They also have a lipogenetic effect which is most evident on trunk, neck and head. All this leads to a redistribution of the fat deposits.

Maximum pharmacologic activity of corticosteroids lags behind peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drugs.

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.

Pharmacokinetics in special patient populations

Hepatic insufficiency

No pharmacokinetic studies have been performed in patients with hepatic impairment. Literature data support that hydrocortisone has an enhanced effect in patients with liver disease as the metabolism and elimination of hydrocortisone is significantly reduced in these patients. Dose reduction should be considered.

5.3 Preclinical safety data

Conventional studies of safety pharmacology and repeated dose toxicity have identified no particular risk. Toxicities observed in repeated dose studies are those expected during continuous exposure to exogenous adrenal cortical steroids.

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

Mutagenicity:
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:
It has been shown that corticosteroids administered to rats reduce fertility.
Corticosteroids have been shown to be teratogenic in many species after administration of doses equivalent to doses used in humans. In animal reproduction studies, glucocorticoids such as methylprednisolone were found to induce malformations (cleft palate, skeletal malformations) and slowed intrauterine growth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Solu-Cortef 100 mg and 250 mg powder and solvent for solution for injection:
- Powder for solution for injection (lower compartment of Act-O-Vial): Monobasic Sodium Phosphate Monohydrate - Disodium Phosphate Anhydrous, and Sodium Hydroxide.
- Solvent for solution for injection (upper compartment of Act-O-Vial): Water for Injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unreconstituted product:
Do not use this product after the expiry date which is stated on the carton label after EXP:. The expiry date refers to the last day of that month.
Shelf life:
Solu-Cortef 100 mg powder and solvent for solution for injection (Act-O-Vial): 24 months.

Solu-Cortef 250 mg powder and solvent for solution for injection (Act-O-Vial): 30 months.

Solution reconstituted with Act-O-Vial: the solution is to be used immediately after reconstitution.

6.4 Special precautions for storage

Unreconstituted product:
Store Below 30 °C.

Reconstituted solution:
- Act-O-Vial: do not freeze and protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pack sizes: Solu-Cortef 100 mg and 250mg, powder and solvent for solution for injection: 1 Act-O-Vial (2 ml)*

*Act-O-Vial: a 2 compartments vial which allows a simple and instant preparation of the sterile solution.

6.6 Special precautions for disposal and other handling

Preparation of solutions:
Parenteral medicines must be inspected visually before administration for the possible presence of particles and discoloration.

Directions for use of the Act-O-Vial
1. Press down the plastic cap to force solvent into the lower compartment.
2. Gently agitate to complete dissolving.
3. Remove plastic protective strip.
4. Sterilize the rubber stopper.

Note: Steps 1-4 must be completed before proceeding.

5. Insert needle squarely through center of stopper until tip is just visible in the lower compartment.
6. Turn the vial and draw up the required dose.

Intravenous or intramuscular injection:
Act-O-Vial pack sizes: prepare the solution as described above.
pack sizes with powder for solution injection: Add the required amount of diluent (bacteriostatic water for injection, isotonic saline solution...) to the vial containing sterile powder under aseptic conditions.

Intravenous infusion:
First prepare the solution as described above.
The 100 mg solution may then be added to 100 - 1000 ml aqueous 5 % glucose solution (or isotonic saline solution or 5 % glucose in an isotonic saline solution if the patient is not on a sodium diet).

The 250 mg solution may be added to 250 - 1000 ml

In cases where administration of small volumes of liquid is desired, 100 mg to 3000 mg Solu-Cortef may be added to 50 ml of the above-mentioned diluents. The resulting solutions remain stable for at least 4 hours and may be administered either directly or by means of IV "piggy-back".

The pH of the reconstituted solution, prepared as described above, is between 7 and 8.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
Pfizer S.A., Belgium.

Manufactured, Packed & Released by
Pfizer Manufacturing Belgium NV, Belgium

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01-Jan-1983

9. DATE OF REVISION OF THE TEXT

December 2025