SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SOLU-CORTEF® 100 mg Injection

SOLU-CORTEF® 100 mg Injection (Act-O-Vial)

SOLU-CORTEF® 500 mg Injection (Act-O-Vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SOLU-CORTEF 100 mg Injection: Each vial contains hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone.

SOLU-CORTEF 100 mg Act-O-Vial: A two-compartment vial containing per 2 mL (when mixed), hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone.

SOLU-CORTEF 500 mg Act-O-Vial: A two-compartment vial containing per 4 mL (when mixed), hydrocortisone sodium succinate equivalent to 500 mg hydrocortisone.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

SOLU-CORTEF 100 mg Injection

White to off-white powder or caked powder.

SOLU-CORTEF 100 mg and 500 mg Act-O-Vial

A two-compartment glass vial. The upper compartment contains a clear, colourless solution and the lower compartment contains a white to off-white powder or caked powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sterile SOLU-CORTEF is indicated in corticosteroid responsive conditions when the oral route of corticosteroid administration is not suitable.

- Acute adrenocortical insufficiency
- Prior to and immediately after bilateral adrenalectomy
- Severe shock
    - In severe shock adjunctive use of intravenous SOLU-CORTEF may aid in achieving haemodynamic restoration. Corticoid therapy should not replace standard methods of combating shock. For information on the use of SOLU-CORTEF in septic shock, refer to section 4.4.
- Acute hypersensitivity reactions
    - In *status asthmaticus*, and allergic medicine anaphylactic reactions, epinephrine (adrenaline) should be given before or along with SOLU-CORTEF.

4.2 Posology and method of administration

SOLU-CORTEF 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 period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

Posology

Therapy is initiated by administering SOLU-CORTEF intravenously over a period of one to several minutes. In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilised – 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 massive hydrocortisone therapy must be continued beyond 48 – 72 hours, hypernatraemia may occur. Under such circumstances it may be desirable to replace SOLU-CORTEF with a corticoid such as methylprednisolone sodium succinate which causes little or no sodium retention.

In other situations in which adequate preparations with intramuscularly administered cortisone or hydrocortisone cannot be accomplished, the initial dose is 100 to 500 mg, depending on the severity of the condition, administered by intravenous injection over a period of at least 30 seconds.

This dose may be repeated at intervals of 1, 3, 6 and 10 hours, as indicated by the patient's response and clinical condition.

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

SOLU-CORTEF therapy is an adjunct to, and not a replacement for, conventional therapy.

Special populations

Hepatic impairment

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

Paediatric population

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 mass, but should not be less than 25 mg daily.

Method of administration

For intravenous injection, intravenous infusion or intramuscular injection.

SOLU-CORTEF is not recommended for intrathecal or epidural use.

For instructions on reconstitution and dilution of the product before administration, see section 6.6.

4.3 Contraindications

SOLU-CORTEF is contraindicated:

- in patients with known hypersensitivity to hydrocortisone sodium succinate or any of the excipients of SOLU-CORTEF listed in section 6.1
- in patients who have systemic fungal infections
- in patients with a traumatic brain injury

Except when used for short-term or emergency therapy as in acute sensitivity reactions, SOLU-CORTEF is absolutely contraindicated in patients with herpes simplex keratitis, acute psychoses, and in patients with latent, healed or arrested tuberculosis. However, concurrent administration of corticoids with antituberculous medicines may be lifesaving in certain cases of meningeal tuberculosis. The following conditions are considered to be relative contraindications: active or latent peptic ulcer, Cushing's syndrome, diverticulitis, recent intestinal anastomoses, osteoporosis, renal insufficiency, thromboembolic tendencies, psychotic tendencies, diabetes mellitus, hypertension, local or systemic infections including vaccinia and varicella, as well as fungal diseases and other exanthematous diseases.

Pregnancy is a relative contraindication to corticoid therapy particularly during the first trimester because of the observation of foetal abnormalities in experimental animals. If it is necessary to give corticosteroids during pregnancy, the newborn infant should be observed closely for signs of hypoadrenalism and appropriate therapy instituted if such signs are present.

If corticoids are employed in the above conditions the risks should be weighed against possible benefits.

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

4.4 Special warnings and precautions for use

SOLU-CORTEF should be given only with full knowledge of the characteristic activity of, and the varied responses to adrenocortical hormones.

Endocrine effects

In patients on corticosteroid therapy subjected to unusual stress, increased dosage or 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. Medicine induced secondary adrenocortical insufficiency may therefore be minimised 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.

Immunosuppressant effects / Increased susceptibility to infections

Corticosteroids such as SOLU-CORTEF may increase susceptibility to infection, may mask signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise 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 medicines that affect cellular immunity, humoral immunity, or neutrophil function. These infections can be severe and may be fatal. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

The use of SOLU-CORTEF 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.

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

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 reported to have both beneficial and detrimental effects. Their routine use in septic shock is not recommended, and a systematic review concluded that use of short-course, high-dose corticosteroids was not supported by the data. 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.

Hypersensitivity reactions may occur, including skin reactions and anaphylactic/anaphylactoid reactions (e.g. bronchospasm). Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any medicine.

Hepato-biliary effects

Hepato-biliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring is required. SOLU-CORTEF may have increased adverse effects in patients with liver disease since the metabolism and elimination of hydrocortisone is significantly decreased in these patients.

Ocular effects

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible 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.

Cardiac effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia 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.

Corticosteroids should be used with caution in patients with hypertension.

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.

Patients and/or caregivers should be warned that 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. Patients/caregivers should be encouraged to seek medical advice if worrying psychological symptoms develop, 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.

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. The onset of symptoms is usually gradual. The symptoms may include back pain and sensory or motor disorders.

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 haemorrhage 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 ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections, also in diverticulitis, intestinal anastomoses, or active or latent peptic ulcer.

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 neuromuscular blocking medicines (e.g. pancuronium). This acute myopathy is generalised, 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.

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. If possible, abrupt cessation of corticosteroid therapy should be avoided because of the danger of superimposed adrenocorticoid insufficiency on the infectious process. Continued supervision of the patient after cessation of SOLU-CORTEF therapy is essential, since there may be a sudden re-appearance of severe manifestations of the disease for which the patient was treated.

Co-treatment with CYP3A inhibitors, including cobicistat-containing medicines, 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).

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

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

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 SOLU-MEDROL compared to placebo.

While a retardant effect on wound healing is seldom encountered, except in high doses, it should be a matter of consideration when SOLU-CORTEF is administered in conjunction with surgery.

SOLU-CORTEF can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

SOLU-CORTEF can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. Corticosteroids increase calcium excretion.

Since spontaneous remission of some diseases, such as rheumatoid arthritis, may occur during pregnancy, every effort should be made to avoid hormone treatment in pregnancy.

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

Paediatric population

Growth may be suppressed in children receiving long-term glucocorticoid therapy. 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 SOLU-CORTEF to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

The following applies only to the Act-O-Vial (where benzyl alcohol is included in the diluent)

The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in paediatric patients.

The minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys’ capacity to detoxify the chemical. Premature and low-birth weight infants are more likely to develop toxicity.

4.5 Interaction with other medicines and other forms of interaction

SOLU-CORTEF is metabolised by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and the cytochrome P450 (CYP) 3A4 enzyme. The CYP3A4 enzyme catalyses 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other medicines 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 SOLU-CORTEF. In the presence of a CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin, and grapefruit juice), the dose of SOLU-CORTEF may need to be decreased to avoid steroid toxicity.

CYP3A4 inducers

May increase hepatic clearance and decrease the plasma concentrations of SOLU-CORTEF. In the presence of a CYP3A4 inducer (e.g. rifampicin, carbamazepine, phenobarbital (phenobarbitone), and phenytoin), the dose of SOLU-CORTEF may need to be increased to achieve the desired response.

CYP3A4 substrates

In the presence of another CYP3A4 substrate, the hepatic clearance of SOLU-CORTEF may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either medicine alone may be more likely to occur with co-administration.

Non-CYP3A4-mediated effects

Other interactions and effects that occur with SOLU-CORTEF are described in Table 1 below.

Table 1 provides a list and descriptions of the most common and/or clinically important medicine interactions or effects with SOLU-CORTEF.

Table 1. Important medicine or substance interactions/effects with SOLU-CORTEF

Medicine class or type *- MEDICINE or SUBSTANCE*	*Interaction/effect*
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
Antibiotic, antitubercular - RIFAMPICIN	CYP3A4 INDUCER (see CYP3A4 inducers above for the results of the interaction).
Anticoagulants (oral)	The effect of SOLU-CORTEF 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 - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE) (see CYP3A4 inducers and CYP3A4 substrates above for the results of the interaction).

Anticonvulsants - PHENOBARBITAL (PHENOBARBITONE) - PHENYTOIN	CYP3A4 INDUCERS (see CYP3A4 inducers above for the results of the interaction).
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking ~~drugs~~ medicines (see section 4.4). 2) Antagonism of the neuromuscular blocking effects of 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 medicines may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Antifungals - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).

Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction). 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. Steroids are also known inducers of CYP enzymes in animal models and *in vitro* studies. Dexamethasone, at doses similar to those used in clinical practice, has been shown to increase CYP3A4 activity in both healthy volunteers and human hepatocyte cultures. Therefore, corticosteroids may induce the metabolism of HIV-protease inhibitors by upregulation of CYP3A4.
Pharmacokinetic enhancers - COBICISTAT	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
Aromatase Inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium channel blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).

Cardiac glycosides - DIGOXIN	Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalaemia. In all patients taking any of these medicine therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Estrogens (including oral contraceptives containing estrogens)	CYP3A4 INHIBITOR (and SUBSTRATE) Estrogens may potentiate effects of SOLU-CORTEF by increasing the concentration of transcortin and thus decreasing the amount of SOLU-CORTEF available to be metabolised. Dosage adjustments of SOLU-CORTEF may be required if estrogens are added to or withdrawn from a stable dosage regimen.
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
Immunosuppressant - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction). Increased activity of both ciclosporin and SOLU-CORTEF may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES (see CYP3A4 substrates above for the results of the interaction).
Macrolide antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction)
Macrolide antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 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 medicines	When corticosteroids are administered concomitantly with potassium-depleting medicines (i.e. diuretics), patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia 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

Pregnancy

Safety in pregnancy and lactation has not been demonstrated.

Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause foetal malformations.

SOLU-CORTEF is teratogenic in animals.

Corticosteroids readily cross the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency (see section 4.3). 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 minimised by administering lower corticosteroid doses.

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

The following applies to the Act-O-Vial (where benzyl alcohol is included in the diluent)

Benzyl alcohol can cross the placenta (see section 4.4).

Breastfeeding

Safety has not been demonstrated.

Corticosteroids are excreted in breast milk.

Fertility

Corticosteroids have been shown to impair fertility in animal studies.

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 may occur during treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

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.

The following adverse reactions are listed by system organ class and ranked by frequency where possible, using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Adverse reactions table

System organ class	*Frequency*	*Adverse reactions*
Infections and infestations	Common	Infections
	Not known	Opportunistic infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
Blood and lymphatic system disorders	Not known	Leucocytosis

Immune system disorders	Rare	Medicine hypersensitivity anaphylactic reaction; anaphylactoid reaction
Endocrine disorders	Common	Cushingoid; hypopituitarism
Metabolism and nutrition disorders	Common	Sodium retention; impaired glucose tolerance; diabetes mellitus
	Uncommon	Fluid retention; hypokalaemic alkalosis; metabolic acidosis
	Not known	Increased insulin requirement (or oral hypoglycaemic medicines in diabetics)
Psychiatric disorders	Uncommon	Affective disorder (including depression, euphoric mood, affect lability, medicine dependence, suicidal ideation), personality change, mood swings, insomnia
Nervous system disorders	Rare	Increased intracranial pressure

	Not known	Spinal epidural lipomatosis with neurological deficits/paraesthesia/ paralysis; benign intracranial hypertension; seizure
Eye disorders	Uncommon	Cataract; exophthalmos
	Not known	Central serous chorioretinopathy with retinal detachment
Cardiac disorders	Not known	Congestive cardiac failure (in susceptible patients)
Vascular disorders	Common	Hypertension
	Not known	Venous thrombosis
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism; Gasping Syndrome
Gastrointestinal disorders	Uncommon	Peptic ulcer (with possible perforation and haemorrhage); pancreatitis
	Not known	Gastric haemorrhage; oesophagitis; intestinal perforation
Skin and subcutaneous tissue disorders	Common	Petechiae
	Uncommon	Skin atrophy
	Rare	Urticaria
	Not known	Ecchymosis
	Common	Osteoporosis; growth retardation

Musculoskeletal and connective tissue disorders	Uncommon	Osteonecrosis; myopathy; bone fracture
	Not known	Muscular weakness
Reproductive system and breast disorders	Not known	Irregular menstruation; amenorrhoea
General disorders and administration site conditions	Uncommon	Impaired healing
Investigations	Common	Decreased carbohydrate tolerance; decreased blood potassium
	Uncommon	Increased intraocular pressure; increased urine calcium
	Not known	Increased alanine aminotransferase (ALT); increased aspartate aminotransferase (AST); increased blood alkaline phosphatase (ALP); suppression of reactions to skin tests
Injury, poisoning and procedural complications	Uncommon	Tendon rupture (particularly of the Achilles tendon)
	Not known	Spinal compression fracture

Post-marketing experience

System Organ Class	Undesirable effect
Endocrine disorders	Steroid withdrawal syndrome
Metabolism and nutrition disorders	Dyslipidaemia, lipomatosis, increased appetite, increased weight
Psychiatric disorders	Psychotic disorder (including mania, delusion, hallucination and schizophrenia), mental disorder, confusional state, anxiety, abnormal behaviour, irritability
Nervous system disorders	Amnesia, cognitive disorder, dizziness, headache
Eye disorders	Glaucoma
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Hiccups
Gastrointestinal disorders	Abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea

Skin and subcutaneous tissue disorders	Angioedema, hirsutism, erythema, hyperhidrosis, skin striae, rash, pruritus, acne, skin hypopigmentation
Musculoskeletal and connective tissue disorders	Myalgia, muscle atrophy, neuropathic arthropathy, arthralgia
General disorders and administration site conditions	Peripheral oedema, fatigue, malaise, injection site reaction
Investigations	Increased blood urea

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no clinical syndrome of acute overdosage with SOLU-CORTEF.

Hydrocortisone is dialysable.

In the event of overdosage, no specific antidote is available. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.5 Corticosteroids

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 analogues 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. After IV injection, pharmacological activity may be 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)

AUC0-∞ = 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, 1 095, and 1 854 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 %.

Biotransformation

Hydrocortisone (i.e., cortisol) is metabolised 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.

Elimination

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monobasic sodium phosphate monohydrate

Dibasic sodium phosphate dried

Benzyl alcohol (preservative) 0,9 % m/v (Act-O-Vial)

Water for injection (Act-O-Vial)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months for 100 mg injection

36 months for 100 mg injection (Act-O-Vial)

60 months for 500 mg injection (Act-O-Vial)

6.4 Special precautions for storage

SOLU-CORTEF 100 mg Injection

Store unreconstituted medicine between 15 °C – 30 °C.

While solutions, when reconstituted as directed, are relatively stable between 15 °C – 30 °C and below, if protected from light, unused solutions prepared with Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride injections, should be discarded after 3 days.

SOLU-CORTEF 100 mg and 500 mg Act-O-Vial

Store unreconstituted medicine between 15 °C – 30 °C.

While solutions, when reconstituted as directed, are relatively stable between 15 °C – 30 °C and below, if protected from light, unused solutions should be discarded after 3 days.

6.5 Nature and contents of container

SOLU-CORTEF 100 mg Injection: 100 mg vial

SOLU-CORTEF 100 mg Act-O-Vial: 2 mL Act-O-Vial

SOLU-CORTEF 500 mg Act-O-Vial: 4 mL Act-O-Vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

SOLU-CORTEF 100 mg Injection

Preparation of solutions

For intravenous or intramuscular injection, prepare the 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 1 000 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).

SOLU-CORTEF Injection, Act-O-Vial system

Directions for using the Act-O-Vial system

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering centre of stopper.
4. Sterilise top of stopper with a suitable germicide.
5. Insert needle squarely through centre of plunger-stopper until tip is just visible.
6. Invert vial and withdraw the required dose.

Further dilution is not necessary for intravenous or intramuscular injection.

For intravenous infusion, first prepare the solution as described above. The solution may then be added to 100 to 1 000 mL of 5 % dextrose in water (or isotonic saline solution or 5 % dextrose in isotonic saline solution if patient is not on sodium restriction).

Important

While solutions when reconstituted as directed are relatively stable at 15 °C – 30 °C and below, and if protected from light, unused solutions should be discarded after 3 days.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION/REFERENCE NUMBERS

SOLU-CORTEF 100 mg: G2957 (Act 101/1965)

SOLU-CORTEF 500 mg: G/21.5/201

9. DATE OF FIRST AUTHORISATION

SOLU-CORTEF 100 mg: Not applicable – Old medicine

SOLU-CORTEF 500 mg: 09 April 1975

10. DATE OF REVISION OF THE TEXT

To be advised

BOTSWANA: S2

SOLU-CORTEF 100 mg - Reg. No.: B9312150

SOLU-CORTEF 500 mg - Reg. No.: B9312155

NAMIBIA: NS2

SOLU-CORTEF 100 mg - Reg. No.: 14/13.4.1/0441

SOLU-CORTEF 500 mg - Reg. No.: 90/20.1.5/001358

ZIMBABWE: PP

SOLU-CORTEF 100 mg - Reg. No.: 80/21.5.1/1151

REFERENCES

Ref No	Description
NA	Module 1.10.3, UK SmPC Solu-Cortef 100 mg, version 42.0, dated 24 December 2021
NA	Module 1.0, Attachment, PRAC recommendations, EMA/PRAC/700146/2016 Corr, 10 November 2016
NA	Module 1.0, Attachment, Hydrocortisone CMDh position EMA/ CMDh/ 217887/ 2020, 30 April 2020
15	Module 2.5, Clinical Overview, Benzyl alcohol excipient warning update to support multiple product CDSs, October 2015
16	Module 2.5, Clinical Overview, To support updates to the Core Data Sheet, November 2016
20	Module 2.5, Clinical Overview, To support updates to section 4.5 Interaction with other medicinal products and other forms of interaction of the Core Data Sheet, October 2017
21	Module 2.5, Clinical Overview, To support updates to section 4.4 and section 4.8 of the Core Data Sheet, August 2020