Solu-Cortef™
Act-O-Vial™
Sterile powder
(Hydrocortisone)

1. NAME OF THE MEDICINE
Hydrocortisone sodium succinate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Hydrocortisone sodium succinate is a white or nearly white, odourless, hygroscopic amorphous solid. It is very soluble in water and in alcohol, very slightly soluble in acetone and insoluble in chloroform.

SOLU-CORTEF powder for injection is available in several packs for intravenous (IV) or intramuscular (IM) administration.

3. PHARMACEUTICAL FORM
SOLU-CORTEF™ Sterile powder 100 mg two-compartment vial.
Each 2 mL Act-O-Vial™ contains:

I. Powder compartment: Hydrocortisone (as hydrocortisone sodium succinate) 100 mg – Sodium biphosphate monohydrate – Dibasic sodium phosphate
II. Diluent compartment: Water for injection.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Endocrine Disorders
- Primary or secondary adrenocortical insufficiency
- Acute adrenocortical insufficiency
- Pre-operatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.
- Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected
- Congenital adrenal hyperplasia
- Non-suppurative thyroiditis
- Hypercalcemia associated with cancer

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

- Synovitis of osteoarthritis

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

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

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

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

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

Respiratory Diseases
- Aspiration pneumonitis
- Berylliosis

- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.
- Loeffler's syndrome not manageable by other means.
- Symptomatic sarcoidosis

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

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

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

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

4.2 Dose and method of administration

Adults
This preparation may be administered by intravenous injection or infusion, or by intramuscular injection. The preferred method for initial emergency use is intravenous injection. Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Therapy is initiated by administering the drug intravenously over a period of 30 seconds (e.g., hydrocortisone sodium succinate equivalent to 100 mg of hydrocortisone) to 10 minutes (e.g., 500 mg or more).

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

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

In general, high-dose corticosteroid therapy should be continued only until the patient's condition has stabilized -- usually not beyond 48 to 72 hours. Although adverse effects associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic

antacid therapy may be indicated.

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

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

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

This dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient's response and clinical condition. While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily.

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

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

Dosage adjustment in hepatic impairment
In patients with liver disease, there may be an increased effect of hydrocortisone resulting from decreased metabolism and elimination of the drug, and reduced dosing may be considered. Monitoring the clinical response to hydrocortisone in these patients should be considered (see section **4.4 Special warnings and precautions for use**).

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

Directions for using the Act-O-Vial™ two compartment vial
1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.

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

5. Insert needle squarely through center of stopper until tip is just visible.
   Invert vial and withdraw dose.

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

4.3 Contraindications

SOLU-CORTEF (hydrocortisone sodium succinate) is contraindicated:

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

Administration of live or live-attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (also see section **4.4 Special warnings and precautions for use**).

SOLU-CORTEF (hydrocortisone sodium succinate) is not indicated for intrathecal, epidural or local injection, or any other unspecified route of administration.

4.4 Special warnings and precautions for use

Immunosuppressant effects/increased susceptibility to infections

Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

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

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. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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

Controlled clinical trials have failed to establish the efficacy of SOLU-MEDROL® (methylprednisolone sodium succinate) in the treatment of sepsis syndrome and septic shock. Two studies suggest that treatment of these conditions with SOLU-MEDROL may increase the risk of mortality in certain patients (i.e. patients with elevated serum creatinine levels or patients

who develop secondary infections after receiving SOLU-MEDROL). Although this trial used SOLU-MEDROL only, Pfizer recommends that SOLU-CORTEF not be used for septic shock or sepsis syndrome either.

Immune system effects
Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions (e.g., bronchospasm) have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

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

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of corticosteroid therapy.

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

Drug-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. 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 corticosteroids. 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.

High doses of corticosteroids can produce or aggravate Cushing’s syndrome. Careful consideration and/or consultation with an endocrinologist are recommended when administering hydrocortisone to patients with Cushing’s disease.

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

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

Psychiatric effects
Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms

typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Nervous system effects
Corticosteroids should be used with caution in patients with seizure disorders.

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

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

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

Ocular effects
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible risk of corneal perforation.

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

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

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.

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 patients with congestive heart failure.

Hypertrophic cardiomyopathy has been reported after administration of hydrocortisone to prematurely born infants, therefore appropriate investigation should be undertaken in order to monitor cardiac function and structure in this patient population.

Vascular effects

Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Steroids should be used with caution in patients with hypertension.

Gastrointestinal effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids *per se* are responsible for peptic ulcers encountered during therapy; however, corticosteroid 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 non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh 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 anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Corticosteroids should be used with caution in patients with osteoporosis.

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

Injury, poisoning and procedural complications
Systemic corticosteroids are not indicated for, and should therefore, not be used to treat traumatic brain injury. A large multicentre randomised study in patients administered corticosteroid therapy after significant head injury revealed an increased risk of mortality in the corticosteroid group compared to the placebo group.

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 corticosteroids should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual.

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section **4.5 Interactions with other medicines and other forms of**

interactions).

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

Use in hepatic impairment
Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring is required.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

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

Use in renal impairment
Corticosteroids should be used with caution in patients with renal insufficiency.

Use in the elderly
No data available.

Paediatric use
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 of glucocorticoid therapy and use of such a regimen should be restricted to the most serious indications. Alternate-day glucocorticoid therapy usually avoids or minimises this side effect.

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

High doses of corticosteroids may produce pancreatitis in children.

Effects on laboratory tests
No data available.

4.5 Interactions with other medicines and other forms of interactions
Hydrocortisone 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 compounds are also substrates of CYP3A4, some of which have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS - May decrease hepatic clearance and increase the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, and grapefruit juice), the dose of hydrocortisone may need to be decreased to avoid steroid toxicity.

CYP3A4 INDUCERS - May increase hepatic clearance and decrease the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inducer (e.g., rifampin, carbamazepine,

phenobarbital, and phenytoin), the dose of hydrocortisone may need to be increased to achieve the desired response.

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

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

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

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

Drug Class or Type - DRUG or SUBSTANCE	**Interaction/Effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL (PHENOBARBITONE) - PHENYTOIN	CYP3A4 INDUCERS
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 (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. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)

Drug Class or Type **- DRUG or SUBSTANCE**	**Interaction/Effect**
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 endocrine 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 hypokalaemia. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHISTERONE	CYP3A4 INHIBITOR (and SUBSTRATE)
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) Increased activity of both ciclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs - 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 Agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e. diuretics), patients should be observed closely for development of hypokalaemia. There is

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
	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.

The pharmacokinetic interactions listed below are potentially clinically important.

1. Oral contraceptives retard the metabolism of hydrocortisone due to its increased binding to globulin (transcortin). This increases the plasma levels of hydrocortisone thus potentiating its biological effect. Dosage adjustments of hydrocortisone may be required if estrogens are added to or withdrawn from a stable dosage regimen.
2. Drugs that induce hepatic enzymes, such as phenobarbitone, phenytoin and rifampicin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response.
3. Drugs, such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No specific animal or clinical studies on the effects of hydrocortisone on fertility have been performed. Corticosteroids have been shown to impair fertility and reduce embryonic viability in studies in mice and rats.

Use in pregnancy

Pregnancy Category C

Since adequate human reproductive studies have not been done with hydrocortisone sodium succinate, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations) and abortion. These findings do not seem to be relevant to human beings. Some corticosteroids readily cross the placenta. Reduced placental and birth weight have been recorded in animals and humans after long-term treatment. Since the possibility of suppression of the adrenal cortex in the newborn baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the fetus when prescribing corticosteroids. 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. The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the fetus or the newborn infant.

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency.

Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

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

during pregnancy.

Use in lactation
Prednisolone is excreted in breast milk, therefore, it is reasonable to assume that all corticosteroids are. No specific data are known for hydrocortisone sodium succinate. Therefore, it is recommended that breastfeeding should cease in women who will be or are receiving corticosteroids.

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

4.8 Adverse effects (undesirable effects)
Infections and infestations
- Infection masked
- Opportunistic infections (with any pathogen, in any location in the body, from mild to fatal
- Infections (becoming active, including reactivation of tuberculosis).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy).

Blood and lymphatic system disorders
- Leucocytosis.

Immune system disorders
- Drug hypersensitivity
- Anaphylactic reaction
- Anaphylactoid reaction.

Endocrine disorders
- Cushingoid
- Hypopituitarism
- Steroid withdrawal syndrome
- Manifestations of latent diabetes mellitus.

Metabolism and nutrition disorders
- Metabolic acidosis
- Sodium retention
- Fluid retention
- Alkalosis hypokalaemic
- Dyslipidaemia
- Glucose tolerance impaired
- Increased insulin requirement (or oral hypoglycaemic agents in diabetics)
- 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
- Intracranial pressure increased
- Benign intracranial hypertension
- Seizure
- Amnesia
- Cognitive disorder
- Dizziness
- Headache.

Eye disorders
- Central serous chorioretinopathy
- Cataract
- Glaucoma
- Exophthalmos
- Vision blurred.

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
- Hiccups.

Gastrointestinal disorders
- Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage)
- Intestinal perforation
- Gastric haemorrhage
- Pancreatitis

- Oesophagitis
- Abdominal distension
- Abdominal pain
- Diarrhoea
- Dyspepsia
- Nausea.

Skin and subcutaneous tissue disorders
- Angioedema
- Hirsutism
- Petechiae
- Ecchymosis
- Skin atrophy
- Erythema
- Hyperhidrosis
- Skin striae
- Rash
- Pruritus
- Urticaria
- Acne
- Skin hypopigmentation.

Musculoskeletal and connective tissue disorders
- Muscle weakness
- Myalgia
- Myopathy
- Muscle atrophy
- Osteoporosis
- Osteonecrosis
- Pathological fracture
- Neuropathic arthropathy
- Arthralgia
- Growth retardation.

Reproductive system and breast disorders
- Menstruation irregular.

General disorders and administration site conditions
- Impaired healing
- Oedema peripheral
- Fatigue
- Malaise
- Injection site reaction.

Investigations
- Intraocular pressure increased
- Carbohydrate tolerance decreased
- Blood potassium decreased
- Urine calcium increased

- Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation
- Blood urea increased
- Suppression of reactions to skin tests.

Injury, poisoning and procedural complications
- Spinal compression fracture
- Tendon rupture.

The following additional reactions are related to parenteral corticosteroid therapy:
- Hyperpigmentation or hypopigmentation
- Subcutaneous and cutaneous atrophy
- Sterile abscess

4.9 Overdose
Symptoms and signs
Reports of acute toxicity and metabolic disturbances with glucocorticoids are rare but do occur. There is no clinical syndrome of acute overdosage with hydrocortisone sodium succinate. Acute overdose may possibly aggravate pre-existing disease states, such as ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes and oedema.

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state. The possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time.

Treatment
In the event of acute overdose, treatment is symptomatic and supportive, including respiratory and cardiovascular function. In chronic toxicity, fluids and electrolytes should be monitored closely. Serum levels are not clinically useful.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Mechanism of action
Hydrocortisone sodium succinate is an anti-inflammatory adrenocortical steroid. This highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly.

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 biological activity

Clinical trials
No data available.

5.2 Pharmacokinetic properties
Absorption
Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within 1 hour and persist for a variable period. This preparation is also rapidly absorbed when administered intramuscularly. Thus, if constantly high blood levels are required, injections

should be made every 4 to 6 hours.

Metabolism
Hydrocortisone 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.

Excretion
Excretion of the intravenously administered dose is nearly complete within 12 hours. Intramuscular injections are excreted in a pattern similar to that observed after intravenous injections.

5.3 Preclinical safety data
Genotoxicity
No data available

Carcinogenicity
No data available

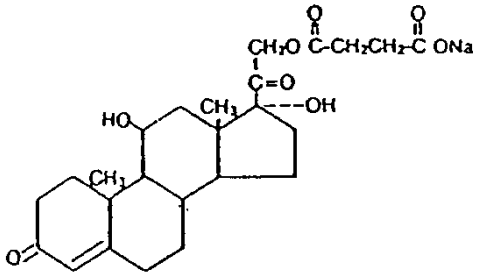
6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Powder: Monobasic Sodium Phosphate Monohydrate, Dibasic Sodium Phosphate Anhydrous, Sodium Hydroxide, Water for Injections.
Diluent: Water for Injections.

6.2 Incompatibilities
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life
Please refer to the outer package for the expiry date.

6.4 Special precautions for storage
Please refer to the outer package for storage condition. Use solution only if it is clear. Single use only. Use immediately and discard unused portion.

6.5 Physicochemical properties
Chemical structure
Non-proprietary name: hydrocortisone sodium succinate



CAS number
The CAS number is 125-04-2 and the molecular weight is 484.52

Pfizer Corporation Hong Kong Limited
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