Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solu-Cortef Powder for Solution for Injection or Infusion 100mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains hydrocortisone sodium succinate 133.7mg equivalent to hydrocortisone 100.0mg. (50mg/ml when reconstituted as recommended)
Excipient with known effect
Each vial contains 10.1 mg of sodium.
For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion
Or
Powder and solvent for solution for injection or infusion
Vial containing white to off-white powder and vial containing sterile water for injections.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solu-Cortef is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1. Endocrine disorders
   Primary or secondary adrenocortical insufficiency.

2. Collagen diseases
   Systemic lupus erythematosus.

3. Dermatological diseases
   Severe erythema multiforme (Stevens-Johnson syndrome).

4. Allergic states
   Bronchial asthma, anaphylactic reactions.

5. Gastro-intestinal diseases
   Ulcerative colitis, Crohn's disease.

6. Respiratory diseases
   Aspiration of gastric contents.

7. Medical emergencies
   Solu-Cortef is indicated in the treatment of shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenocortical insufficiency may be present.

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 being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Dosage usually ranges from 100 mg to 500 mg depending on the severity of the condition, administered by intravenous injection over a period of one to ten minutes. This dose may be repeated at intervals of 2, 4 or 6 hours as indicated by the patient's response and clinical condition.

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 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. If hydrocortisone therapy must be continued beyond 48 to 72 hours hypernatraemia may occur, therefore it may be preferable to replace Solu-Cortef with a corticosteroid such as methylprednisolone sodium succinate as little or no sodium retention occurs.

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see section 4.4).

Undesirable effects may be minimized by using the lowest effective dose for the minimum period (see section 4.4).

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

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

Paediatric population: Dosage should be reduced for infants and children, but should be governed more by the severity of the condition and response of the patient, than by age of size. Dosage should not be less than 25 mg daily (see section 4.4).

Elderly patients: Solu-Cortef is primarily used in acute short-term conditions. When used according to instructions, there is no information to suggest that a change in dosage is warranted in the elderly. However, treatment of elderly patients, particularly if long-term, should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (see section 4.4).

Preparation of solutions: For intravenous or intramuscular injection prepare the solution aseptically by adding not more than 2 ml of sterile water for injections to the contents of one vial of Solu-Cortef 100 mg, shake and withdraw for use.

For intravenous infusion, first prepare the solution by adding not more than 2 ml of sterile water for injections to the vial; this solution may then be added to 100 ml – 1000 ml (but not less than 100 ml) of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

When reconstituted as directed the pH of the solution will range from 7.0 to 8.0

This medicine is not recommended for use by the intrathecal route of administration.

4.3 Contraindications

Solu-Cortef is contraindicated:

- in patients who have known hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in patients who have systemic infection unless specific anti-infective therapy is employed
- 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.

4.4 Special warnings and precautions for use

Special warnings:

1. A Patient Information leaflet is provided in the pack by the manufacturer.

2. Undesirable effects may be minimized by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2).

3. Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute rebound exacerbation of disease, acute adrenal insufficiency or polyarteritis, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any intercurrent illness, trauma, anaesthesia or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

4. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

5. Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions 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 drug allergy.

6. 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. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.

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

8. Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist cared and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

9. Psychiatric effects: Patients and/or carers should be warned that potentially severe psychiatric adverse reactions **may** occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

10. The use of corticosteroids 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 an appropriate

antituberculosis regiment. 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.

11. Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8).

12. Intramuscular injection should avoid the deltoid area because of the possibility of tissue atrophy.

13. 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 (see section 4.2).

14. 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.

15. Ocular Effects: 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. Central serous chorioretinopathy, may lead to retinal detachment. Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

16. 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.

17. Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury: a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

18. 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.

19. 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.

20. Endocrine effects: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels. Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease. There is an enhanced effect of corticosteroids on patients with hypothyroidism.

21. 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.

22. 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.

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).

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

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

24. Corticosteroids should be used with caution in patients with seizure disorders.

25. 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.

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.

Precautions: Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

1. Osteoporosis is generally associated with long-term use and large doses of glucocorticoids. Corticosteroids should be used with caution in patients with osteoporosis (post-menopausal females are particularly at risk).
2. Hypertension.
3. Existing or previous history of severe affective disorders (especially previous steroid psychosis).

4. Corticosteroids, including hydrocortisone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus (or a family history of diabetes).
5. History of tuberculosis.
6. Glaucoma (or a family history of glaucoma).
7. Previous corticosteroid-induced myopathy.
8. Liver failure or cirrhosis.
9. Corticosteroids should be used with caution in patients with renal insufficiency.
10. Epilepsy.
11. Peptic ulceration.
12. Fresh intestinal anastomoses.
13. Predisposition to thrombophlembitis.
14. Abscess or other pyogenic infections.
15. Ulcerative colitis.
16. Diverticulitis.
17. Myasthenia gravis.
18. Exanthematous diseases.

Paediatric population

Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily-divided dose glucocorticoid therapy. The use of such a regimen should be restricted to the most serious indications. Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure. High doses of corticosteroids may produce pancreatitis in children.

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

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

Use in the elderly

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

Excipient information

This medicinal product contains 10.1 mg of sodium, equivalent to 0.5% 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

1. Hydrocortisone is metabolized by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and the c ytochrome 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.
2. 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.
3. 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.

4. 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.
5. 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 corticosteriods 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 - 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)
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.
Pharmacokinetic enhancers -COBICISTAT	CYP3A4 INHIBITORS
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 hypokalemia. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels,

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
	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 - 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 hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs. Hydrocortisone can cross the placenta. There is no evidence that corticosteroids result in an increased incidence of congenital anomalies when given to pregnant women.

There is evidence that administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including: cleft palate; intrauterine growth retardation and affects on brain growth and development. Based on animal studies, there may be a very small risk of cleft palate and intra-uterine growth retardation in the foetus.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids. Neonates of mothers who received such therapy during pregnancy should be observed for signs of hypoadrenalism and appropriate measures instituted if such signs exist. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state. Patients with pre-eclampsia or fluid retention require close monitoring.

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

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

Breast-feeding

Corticosteroids, including hydrocortisone, are excreted in breast milk. Infants of mothers taking pharmacological doses of steroids should be monitored carefully for signs of adrenal suppression. This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

Fertility

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

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 convulsions are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The incidence of predictable undesirable side effects associated with the use of corticosteroids, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and duration of treatment (see section 4.4).

System Organ Class	Frequency	Undesirable Effects
Infections and infestations	**Not Known**	Opportunistic infections, infections.
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**	Leukocytosis
Immune system disorders	**Not Known**	Drug hypersensitivity Anaphylactic reaction; Anaphylactoid reaction
Endocrine disorders	**Not Known**	Cushingoid Hypothalamic pituitary adrenal axis suppression; Steroid withdrawal syndrome
Metabolism and nutrition disorders	**Not Known**	Metabolic acidosis; Sodium retention; Fluid retention; Alkalosis hypokalaemic; Dyslipidaemia; Carbohydrate tolerance decreased; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Increased insulin requirement (or oral hypoglycemic agents in diabetics); Lipomatosis; Increased appetite; Weight gain
Psychiatric disorders	**Not Known**	Affective disorders ((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	**Not Known**	Epidural lipomatosis, Intracranial pressure increased with papilloedema in children (benign intracranial hypertension), Seizure; Amnesia; Cognitive disorder; Dizziness; Headache
Eye disorders	**Not Known**	Central serous chorioretinopathy, Cataracts; Glaucoma; Exophthalmos; Vision blurred (see also section 4.4); Intraocular pressure increased (with possible damage to the optic nerve); Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease;
Ear and labyrinth disorders	**Not Known**	Vertigo
Cardiac disorders	**Not Known**	Cardiac failure congestive (in susceptible patients); Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	**Not Known**	Thrombosis including Thromboembolism; Hypertension; Hypotension
Respiratory, thoracic and mediastinal disorders	**Not Known**	Pulmonary embolism*; Hiccups
Gastrointestinal disorders	**Not Known**	Peptic ulcer (with peptic ulcer perforation and peptic ulcer haemorrhage); Intestinal perforation; Acute pancreatitis; Oesophageal ulceration; Oesophageal candidiasis; Abdominal distension; Abdominal pain;

		Diarrhoea; Dyspepsia; Nausea
Skin and subcutaneous tissue disorders	**Not Known**	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Bruising; Striae; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation; Telangiectasia; Skin hyperpigmentation
Musculoskeletal and connective tissue disorders	**Not Known**	Muscle weakness; Myalgia; Myopathy; Muscle atrophy; Osteoporosis; Avascular Osteonecrosis; Pathological fractures; Neuropathic arthropathy; Arthralgia; Growth retardation
Reproductive system and breast disorders	**Not Known**	Menstruation irregular; Amenorrhoea
General disorders and administration site conditions	**Not Known**	Impaired healing; Oedema peripheral; Fatigue; Abscess sterile; Malaise; Injection site reaction
Investigations	**Not Known**	Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood potassium decreased; Blood alkaline phosphatase increased; Urine calcium increased; Blood urea increased; Suppression of reactions to skin tests*; Weight increased
Injury, poisoning and procedural complications	**Not Known**	Spinal compression fracture; Tendon rupture

*Occurred in subjects at risk of thrombosis/with other risk factors for thrombosis.
* Not a MedDRA PT

Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids.. Following overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. Further traumatic episodes during that period may require special supportive therapy. Hydrocortisone is dialysable. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC Code: H02A B09

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

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

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity.

The highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period.

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

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

5.2 Pharmacokinetic properties

The pharmacokinetics of hydrocortisone in healthy male subjects demonstrated nonlinear kinetics when a single intravenous dose of hydrocortisone sodium succinate higher than 20 mg was administered, and the corresponding pharmacokinetic parameters of hydrocortisone are presented in Table 2

Table 2. Mean (SD) hydrocortisone pharmacokinetic parameters following single intravenous doses

	Healthy Male Adults (21-29 years; N = 6)			
Dose (mg)	5	10	20	40
Total Exposure ($AUC_{0-\infty}$; ng·h/mL)	410 (80)	790 (100)	1480 (310)	2290 (260)
Clearance (CL; mL/min/m^2)	209 (42)	218 (23)	239 (44)	294 (34)
Volume of Distribution at Steady State (V_{dss}; L)	20.7 (7.3)	20.8 (4.3)	26.0 (4.1)	37.5 (5.8)
Elimination Half-life ($t_{1/2}$; hr)	1.3 (0.3)	1.3 (0.2)	1.7 (0.2)	1.9 (0.1)

$AUC_{0-\infty}$ = Area under the curve from time zero to infinity.

Absorption
Following administration of 5, 10, 20, and 40 mg single intravenous doses of hydrocortisone sodium succinate in healthy male subjects, mean peak values obtained at 10 minutes after dosing were 312, 573, 1095, and 1854 ng/mL, respectively. Hydrocortisone sodium succinate is rapidly absorbed when administered intramuscularly.

Distribution
Hydrocortisone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The volume of distribution at steady state for hydrocortisone ranged from approximately 20 to 40 L (Table 2). Hydrocortisone binds to the glycoprotein transcortin (i.e., corticosteroid binding globulin) and albumin. The plasma protein binding of hydrocortisone in humans is approximately 92%.

Biotransformation
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.

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.

5.3 Preclinical safety data

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.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows. Corticosteroids have been shown to reduce fertility when administered to rats. The numbers of implantations and live fetuses were reduced. Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in

resorptions), and intra-uterine growth retardation. With hydrocortisone, cleft palate was observed when administered to pregnant mice and hamsters during organogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for reconstitution:
Sodium dihydrogen phosphate
Disodium phosphate anhydrous
Sodium hydroxide (for pH adjustment)

Solvent for reconstitution:
Water for injection

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

5 years.
The reconstituted product is to be used immediately.
Any remaining solution should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Single packs containing one vial of powder for solution for injection or infusion and one vial of solvent for solution

10 vial pack containing 10 vials of powder for solution for injection or infusion.
Not all pack sizes may be marketed.

Powder for solution for injection or infusion:
Type 1, flint glass vial with butyl rubber plug and metal seal containing the equivalent of 100 mg of hydrocortisone as the sodium succinate salt for reconstitution with water for injections.

Solvent for solution:
Type 1 glass vial with rubber stopper containing 2 ml of water for injections.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of solutions: For intravenous or intramuscular injection prepare the solution aseptically by adding not more than 2 ml of Sterile Water for Injections to the contents of one vial of Solu-Cortef 100 mg, shake and withdraw for use.

For intravenous infusion, first prepare the solution by adding not more than 2 ml of Sterile Water for Injections to the vial; this solution may then be added to 100 ml – 1000 ml (but not less than 100 ml) of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

When reconstituted as directed the pH of the solution will range from 7.0 to 8.0.

See section 4.2. No diluents other than those referred to are recommended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Use solution only if it is clear.

After reconstitution with Water for Injection, use immediately, discard any remaining solution.

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

September 2023