SOLU-CORTEF®
(Hydrocortisone sodium succinate)

1. NAME OF THE MEDICINAL PRODUCT

SOLU-CORTEF®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pack contains hydrocortisone sodium succinate equivalent to hydrocortisone 100 mg, 250 mg or 1 g.

Concentration in the prepared solution:
Solu-Cortef 100 mg: hydrocortisone 50 mg/ml

Solu-Cortef 250 mg: hydrocortisone 125 mg/ml
Excipient with known effect:
Reconstituted solution contains a total 30 mg sodium per 2 mL, equivalent to 15 mg/ml.

Solu-Cortef 1 g: hydrocortisone 125 mg/ml
Excipients with known effect:
Reconstituted solution contains a total 72 mg benzyl alcohol per 8 mL, equivalent to 9 mg/ml.
Reconstituted solution contains a total 109.3 mg sodium per 8 mL, equivalent to 13.66 mg/ml.

For the full list of excipients, see section 6.1. LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Substitution treatment:
In primary or secondary adrenocortical insufficiency and congenital adrenogenital syndrome when oral therapy cannot be carried out, e.g., in acute disease states. In connection with surgery when the glucocorticoid reserve is insufficient.

Non-specific therapy: e.g., for shock of varying causes as a complement to other treatment, anaphylactic reactions, severe allergic conditions and reactions after insect and snake bites, and asthma.

For SLE, congenital adrenocortical hyperplasia, leukaemia and malignant lymphoma.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology

The standard dose is 100 mg hydrocortisone. If no satisfactory response is obtained within 15-30 minutes following intravenous injection or after a slightly longer time following intramuscular injection, a further 100 mg of Solu-Cortef can be given 1, 3, 6 and 10 hours after the initial injection.

In some cases of asthma attacks, better treatment results may be expected with intravenous infusion than with intravenous or intramuscular injection.

The dose 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.

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.

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).

Paediatric population

For severe conditions in *children*, the dose is more dependent on the severity of the condition than on weight and age. Amounts less than 25 mg Solu-Cortef should not be given. Oral treatment with glucocorticoids should replace parenteral therapy as soon as possible.

Patients with hepatic impairment

In patients with liver disease, there may be an increased effect (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE) and reduced dosing may be considered.

Method of administration

Solu-Cortef is intended for intravenous or intramuscular injection.

Not for intrathecal or epidural use.

In exceptional cases, Solu-Cortef can be administered intrathecally as part of some chemotherapy regimens (diluents containing benzyl alcohol must not be used) (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. LIST OF EXCIPIENTS.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious medical events have been reported in connection with intrathecal/epidural administration. Solu-Cortef 1 g powder and solvent for solution for injection contains benzyl alcohol, which in high concentrations can have toxic effects on nerve tissue.

The complications of glucocorticoid treatment depend on the size of the dose and the duration of treatment. The lowest possible corticosteroid dose to keep the disease under control must be used during the treatment.

Immunosuppressive effects/increased susceptibility to infections
Glucocorticoids should not be given in infections without concomitant causal treatment.
Caution should be observed in the case of tuberculosis.

Corticosteroids can increase susceptibility to infection and mask certain signs of infection, and new infections may occur during their use. Resistance may be impaired and the capacity to limit an infection locally may be reduced when using corticosteroids. The frequency of complications from infection increases with the dose of corticosteroids.

Chicken pox and measles are examples of diseases that may have a more serious or even fatal outcome in children or adults who are not vaccinated and who are being treated with corticosteroids.

Kaposi's sarcoma has been reported in patients who are being treated with corticosteroids. Discontinuation of corticosteroid treatment can lead to clinical remission.

Routine use in the event of septic shock is not recommended.

Reactions to skin patch tests may be attenuated.

Immune system disorders
Allergic reactions may occur. As rare cases of skin reactions and anaphylactic/anaphylactoid reactions (e.g. bronchospasm) have occurred in patients who received parenteral treatment with corticosteroids, appropriate precautions must be taken before administration, particularly if the patient has a history of drug allergy.

Endocrine disorders
Acute adrenal insufficiency can occur upon abrupt discontinuation of glucocorticoid treatment after a long period of use. An increased dose of rapid-acting corticosteroids before, during and after a stressful situation is indicated in patients who are receiving corticosteroid treatment and are exposed to abnormal stress.

Medicinal product-caused secondary adrenal insufficiency can be minimised by gradual dose reduction. This type of relative insufficiency can remain for several months after discontinuation of the treatment. Steroid treatment must therefore be recommenced in all stressful situations that occur during this period.

Withdrawal syndrome following steroid treatment may also occur following abrupt discontinuation of glucocorticoids. The syndrome involves symptoms such as fever, joint pain,

myalgia and malaise. These effects are presumably due to the sudden change in glucocorticoid concentration, rather than low corticosteroid levels.

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.

Corticosteroids have an intensified effect on patients with hypothyreosis.

Metabolism and nutrition disorders
Corticosteroids, including hydrocortisone, can increase blood sugar levels. Caution should be observed in the case of diabetes mellitus.

Psychiatric disorders
Psychiatric diseases can occur when corticosteroids are used, varying from euphoria, sleep disorders, mood swings, personality changes and severe depression to direct psychotic manifestations. Previously existing emotional instability or psychotic tendencies can also be exacerbated by corticosteroids.

Nervous system disorders
Corticosteroids must be used with caution in patients with diseases that can cause seizures.

There have been reports of epidural lipomatosis in patients who take corticosteroids, particularly in the event of long-term use of high doses.

Eye disorders
Corticosteroids must be used in caution with patients with herpes simplex of the eyes due to the risk of corneal perforation.

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.

Longer-term use of corticosteroids can provoke anterior subcapsular cataract and nuclear cataract (particularly in children), exophthalmos, or increased intraocular pressure, which can result in glaucoma and potential injury to the visual nerve. Caution should be observed in the case of glaucoma.

Secondary fungal and viral infections in the eyes can be more easily established in patients who receive glucocorticoids.

Cardiac disorders
The side effects of glucocorticoids on the cardiovascular system, e.g. dyslipidaemia and hypertension, can predispose treated patients with existing cardiovascular risk factors to further cardiovascular effects if treatment occurs at high doses and for a longer period. Corticosteroids must therefore be introduced with discretion in these patients, and risk modification and further

monitoring of the cardiac function considered as required. In the event of heart failure, systemic corticosteroids must be used with caution.

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.

Vascular disorders
Thrombosis and venous thromboembolism have been reported with corticosteroid use. Corticosteroids must therefore be used with caution in patients who have or may be predisposed to thromboembolic diseases.

Steroids must be used with caution in patients with hypertension.

Gastrointestinal disorders
High doses of corticosteroids can lead to acute pancreatitis.

Glucocorticoid treatment can mask peritonitis and other signs and symptoms in connection with gastrointestinal diseases, such as perforation, obstruction or pancreatitis. The risk of gastrointestinal ulcers is increased in combination with non-steroidal anti-inflammatory drugs (NSAIDs).

Corticosteroids must be used with caution in non-specific ulcerative colitis if there is an imminent risk of perforation, abscess or pyogenic infections, and also in the event of diverticulitis, new intestinal anastomoses, and active or latent peptic ulcers in the ventricle or duodenum.

Hepatobiliary disorders
Diseases of the liver and biliary tracts have been reported. These diseases may be reversible after discontinuation of the treatment. Appropriate monitoring is required.

Hydrocortisone can have an increased effect on patients with liver disease, as the metabolism and elimination of hydrocortisone are considerably lower in these patients.

Musculoskeletal disorders
Acute myopathy has been described with the use of high doses of corticosteroids, most frequently in patients with neuromuscular transmission diseases (e.g. myasthenia gravis), or in patients who are being simultaneously treated with anticholinergic agents, such as neuromuscular blockers (e.g. pancuronium) (see section 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

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

Renal and urinary disorders
Corticosteroids must be used with caution in patients with reduced kidney function.

Investigations
Hydrocortisone can increase blood pressure and lead to salt and fluid retention, as well as increased secretion of potassium. All corticosteroids increase secretion of calcium.

Injury, poisoning and procedural complications
High doses of systemic corticosteroids must be used to treat traumatic brain injuries.

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

Paediatric population

Growth may be inhibited in children who receive long-term treatment with daily doses of glucocorticoids. Such treatment regimens must therefore be limited to the most serious indications.

Infants and children who receive long-term treatment with corticosteroids are at particularly high risk of increased intracranial pressure.

Information on excipients

Benzyl alcohol
Solu-Cortef 1 g contains benzyl alcohol (see section 2. QUALITATIVE AND QUANTITATIVE COMPOSITION).

The preservative benzyl alcohol can cause hypersensitivity reactions.

Intravenous administration of benzyl alcohol has been associated with severe adverse reactions and death in children including newborns (“gasping syndrome”). Although normal therapeutic doses of this medicinal product lead to significantly lower amounts of benzyl alcohol than have been reported in connection with “gasping syndrome”, the minimum amount of benzyl alcohol causing toxicity is not known. Formulations containing benzyl alcohol should only be used in children if necessary and where no other alternative is available. Premature and low birth weight infants may be more susceptible to the development of toxicity.

Formulations containing benzyl alcohol should not be used for more than 1 week in children under 3 years of age if this is not necessary.

If use of Solu-Cortef is necessary, it is important to monitor the total daily amount of benzyl alcohol from all sources, particularly in patients with impaired liver or kidney function, as well as in pregnant and breast-feeding women, due to the risk of accumulation and toxicity (metabolic acidosis).

Sodium
Solu-Cortef 100 mg contains less than 1 mmol (23 mg) sodium per vial, i.e., it is essentially “sodium free”.

Solu-Cortef 250 mg contains 30 mg sodium per vial, equivalent to 1.5% of the WHO’s highest recommended daily intake (2 grams sodium for adults).

Solu-Cortef 1 g contains 109.3 mg sodium per vial, equivalent to 5.5% of the WHO's highest recommended daily intake (2 grams sodium for adults).

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Hydrocortisone is metabolised by the cytochrome P450 (CYP) 3A4 enzyme. Certain other medicinal products may change glucocorticoid metabolism via induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INDUCERS (e.g. rifampicin, carbamazepine, phenobarbital or phenytoin) – Can increase clearance in the liver and reduce the plasma concentration of hydrocortisone. If a CYP3A4 inducer is taken simultaneously, the hydrocortisone dose may need to be increased in order to achieve the desired treatment response.

CYP3A4 INHIBITORS (e.g. ketoconazole, itraconazole, clarithromycin or grapefruit juice) – Can reduce hepatic clearance and increase the plasma concentration of hydrocortisone.

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.

Anticoagulants (oral) – There have been reports of both an increased and weakened effect of anticoagulants when given simultaneously with corticosteroids. The coagulation index must therefore be monitored to maintain the desired anticoagulating effects.

Anticholinergics – Corticosteroids can change the effect of anticholinergics.
1) Acute myopathy has been reported during simultaneous use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking agents (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction can be expected with all competitive neuromuscular blockers.

Anticholinesterases – Steroids can reduce the effect of anticholinesterases in the case of myasthenia gravis.

Antidiabetics – As corticosteroids can increase blood sugar levels, the dose of antidiabetics may need to be adjusted.

Aromatase inhibitors (aminoglutethimide) – Aminoglutethimide-induced adrenal suppression can exacerbate endocrine changes caused by long-term treatment with glucocorticoids.

Cardiac glycosides (digoxin) – Simultaneous use of corticosteroids and cardiac glycosides can increase the risk of arrhythmia or digitalis toxicity related to hypokalemia. The serum electrolyte levels, in particular potassium content, of all patients who take such combinations of medicinal products must be monitored closely.

NSAIDs (high dose acetylsalicylic acid)
1) The incidence of gastrointestinal bleeding and ulceration may be increased when corticosteroids and NSAIDs are given simultaneously.
2) Corticosteroids can increase clearance of acetylsalicylic acid in high doses, which can lead to lower serum salicylate levels. When corticosteroid treatment is discontinued, this can lead to higher serum salicylate levels, and thus an increased risk of toxic reactions to salicylate.

Potassium-reducing agents – There is an increased risk of hypokalaemia when corticosteroids are given simultaneously with potassium-reducing agents (e.g., diuretics) and the patient should be monitored closely. There is also an increased risk of hypokalemia during simultaneous treatment with amphotericin B, xanthines and beta 2 agonists.

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility:
In animal studies, corticosteroids have been shown to impair fertility (see section 5.3. PRECLINICAL SAFETY DATA).

Pregnancy:
In animal studies corticosteroids, including hydrocortisone, have been shown to cause malformations of various types (cleft palate, skeletal malformations). Corticosteroids do not appear to cause congenital malformations when they are given to pregnant women. As no adequate reproduction studies have been performed in humans with hydrocortisone sodium succinate, this medicinal product must only be used during pregnancy following a careful assessment of the benefit/risk ratio for the mother and the foetus.

After long-term treatment, reduced placental and foetal weights have been confirmed in humans and animals. In addition, in cases of long-term treatment there is a risk of adrenocortical suppression in the new-born child. During pregnancy, therefore, corticosteroids should only be given after careful consideration.

Cataract has been observed in infants whose mothers received long-term treatment with corticosteroids during pregnancy.

Solu-Cortef 1 g contains the preservative benzyl alcohol. Benzyl alcohol can cross to the placenta (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Breastfeeding:
Hydrocortisone passes into breast milk in such amounts that there is a risk of an effect on the child even with therapeutic doses.

This medicinal product must only be used when breast-feeding after a careful evaluation of the benefit/risk ratio for the mother and the child.

Solu-Cortef 1 g contains the preservative benzyl alcohol (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of corticosteroids on the ability to drive and use machines has not been evaluated. Adverse events such as crams might occur in treatment with corticosteroids. If the patient have side effects that influence the attention it should not drive and use machines.

4.8. UNDESIRABLE EFFECTS

The undesirable effects that can occur in long-term therapy with glucocorticoids are very rare with parenteral short-term therapy.

All adverse events are presented in the table below, classified by system organ class and frequency: Common (≥ 1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥ 1/10,000 to <1/1,000) and not known (cannot be estimated from the available data).

Short-term treatment:

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Rare	Allergic reactions, anaphylaxis-like reactions with bronchospasm

Long-term treatment:

System Organ Class	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Uncommon	Increased tendency to coagulation can cause thromboembolic events
	Not known	Leukocytosis (due to a redistribution of intravascular granulocytes)
Immune system disorders	Common	Masking or activation of latent infection and inhibition of defence against infection
	Uncommon	Allergic reactions, anaphylaxis-like reactions with bronchospasm
Endocrine disorders	Common	Hypothalamic pituitary adrenal axis suppression, Cushing-like symptoms, menstrual disturbances, inhibition of growth in children, decreased carbohydrate tolerance, which means that diabetes mellitus can be exacerbated and latent diabetes become manifest
	Not known	Pheochromocytoma related crisis (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Metabolism and nutrition disorders	Common	Hypokalaemia, sodium retention
	Uncommon	Metabolic acidosis, calcium loss
	Not known	Dyslipidaemia, lipomatosis, increased appetite (which may result in weight gain)
Psychiatric disorders	Uncommon	Mental disturbances
	Not known	Affective disorders (including depression, euphoria, emotional lability, drug-dependence, suicidal thoughts), psychiatric disorders (including mania, delusions, hallucinations and schizophrenia), personality changes, sleep disorders, mood swings, confusion, anxiety, abnormal behaviour, irritability
Nervous system disorders	Rare	Increased intracranial pressure, pseudotumor cerebri
	Not known	Epidural lipomatosis, amnesia, cognitive disorder, dizziness, headache, seizures
Eye disorders	Uncommon	Increased intraocular pressure, posterior cataract,

		exophthalmia
	Not known	Central serous chorioretinopathy, vision blurred
Cardiac disorders	Not known	Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Common	Oedema, hypertension, cardiac incompensation
Respiratory tract, thoracic and mediastinal disorders	Not known	Hiccups
Gastrointestinal disorders	Uncommon	Peptic ulcer, perforation and possibly haemorrhage, pancreatitis
	Not known	Distended abdomen, abdominal pain, diarrhoea, dyspepsia, nausea
Skin and subcutaneous tissue disorders	Common	Petechiae
	Uncommon	Skin atrophy, impaired wound healing
	Not known	Angioedema, hirsutism, erythema, hyperhidrosis, striae, skin rash, pruritus, acne, hypopigmentation
Musculoskeletal and connective tissue disorders	Common	Muscle atrophy, osteoporosis
	Uncommon	Aseptic bone necrosis, myopathy, spontaneous fractures, tendon rupture
	Not known	Myalgia, neuropathic arthropathy, arthralgia
General disorders and/or administration site conditions	Not known	Tiredness, malaise, injection site reaction
Investigations	Not known	Increase in blood urea, weight increased

Effects on the liver have been observed in connection with corticosteroid treatment. These changes are usually small, not associated with clinical symptoms, and are reversible on discontinuation of treatment.

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.

4.9. OVERDOSE

Toxicity and symptoms: Acute toxicity even with massive doses of corticosteroids does not generally constitute a clinical problem. Acute overdose may possibly aggravate pre-existing conditions such as ulcer, electrolyte disturbances, infections, oedema.

Treatment: There is no specific antidote to overdose. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: corticosteroids for systemic use - glucocorticoid
ATC code: H02A B09

Glucocorticoids, both naturally-occurring and synthetic, are adrenocortical steroids.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as substitution treatment in adrenocortical failure conditions. Their synthetic analogues are primarily used for their anti-inflammatory effect in multiple organ system diseases.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory effect as hydrocortisone. When it is given parenterally and in equimolar quantities, the two compounds are equivalent as regards biological activity. The sodium succinate ester of hydrocortisone, which is easily soluble in water, means that intravenous administration of high doses of hydrocortisone can take place immediately in small volumes of solvent. Following intravenous injection of hydrocortisone sodium succinate, effects can be observed within one hour and remain for varying amounts of time.

Glucocorticoids have deep and varying metabolic effects. They also change the body's immune response to various stimuli.

The relative potency of methyl prednisolone sodium succinate and hydrocortisone sodium succinate following intravenous administration, which is demonstrated by the reduced number of eosinophils, is five to one. This agrees with the ratio of methylprednisolone to hydrocortisone as regards oral potency.

5.2. PHARMACOKINETIC PROPERTIES

Absorption
Hydrocortisone is rapidly absorbed in intramuscular administration.

Distribution
Hydrocortisone is distributed to a significant extent in the tissues, passes the blood-brain barrier and is excreted in breast milk. In steady-state, distribution volume for hydrocortisone varies from approximately 20 to 40 L. Hydrocortisone binds to the glycoprotein transcortin (i.e., corticosteroid-binding globulin) and albumin. Plasma protein-binding for hydrocortisone is approximately 90 % at low and normal doses, while it decreases with higher doses. This gives dose-dependent pharmacokinetics, with increased clearance and a reduced half-life with increased doses.

Biotransformation
Hydrocortisone (i.e. cortisol) is metabolised by 11β-HSD2 into cortisone, and then into dihydrocortisone, tetrahydrocortisone and other metabolites. Cortisone can be converted into cortisol by 11β-hydroxysteroid hydrogenase type 1 (11β-HSD2). Hydrocortisone is also metabolised by CYP3A4 into 6β-hydroxycortisol (6β-OHF).

Elimination
Metabolism occurs in the liver and the metabolites are primarily excreted via the kidneys. The half-life is 1-2 hours. The administered dose is practically totally eliminated within 12 hours.

5.3. PRECLINICAL SAFETY DATA

Carcinogenic properties:
Hydrocortisone did not increase tumour incidence in male and female rats during a two-year carcinogenicity study.

Mutagenic properties:
Corticosteroids, a class of steroid hormones that includes hydrocortisone, consistently demonstrate negative results in bacterial mutagenicity analyses. Hydrocortisone and dexamethasone induced chromosomal deviations in human lymphocytes *in vitro* and in mice *in vivo*. The biological relevance of these results is, however, unclear, as hydrocortisone did not increase the tumour incidence in male or female rats during a two-year carcinogenicity study. Fludrocortisone (9α-fluorohydrocortisone, structurally similar to hydrocortisone) was negative in the analysis of chromosome deviations in human lymphocytes.

Reproductive toxicity:
Corticosteroids have been shown to impair fertility when they were administered to rats. Male rats received corticosterone in doses of 0.10 and 25 mg/kg/day via subcutaneous injection once daily for 6 weeks. They were mated with untreated female rats. The high dose was reduced to 20 mg/kg/day after day 15. Fewer mating plugs were observed, which may have been secondary to atrophic effects on secondary gonads. The number of implantations and living foetuses was lower.

Corticosteroids have been shown to have a teratogenic effect on many species of animal when they are given in doses that are equivalent to the dose in humans. In animal reproduction studies, glucocorticoids have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryofoetal mortality (i.e., increased number of resorptions) and intrauterine growth inhibition. When using hydrocortisone, cleft palate was observed when the substance was administered to pregnant mice and hamsters during organogenesis.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Powder:
Sodium dihydrogen phosphate monohydrate, sodium hydroxide, sodium phosphate.

Solvent:
100 mg and 250 mg
Water for injections.

1 g
Benzyl alcohol, water for injections.

6.2. INCOMPATIBILITIES

When mixed with other liquids there is a risk of precipitation at low pH values. With pH values above 8 there is hydrolysis but without precipitation.

6.3. SHELF LIFE

Pack (Nature & Content of Container)	**Shelf-life**	**Storage Conditions**
Vial, clear glass (1 vial)	Solu Cortef 100mg	Store at 25°C – 30°C.

	Injection: 36 Months Solu Cortef 250mg & 500mg Injection: 60 Months	

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package in order to protect from moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

Combination packs, Act-O-Vial, glass vial with two compartments: the upper part contains solvent (2 ml in 100 mg and 250 mg-packs, 8 ml in 1 g-pack) and the lower contains powder.
100 mg: 1x100 mg, 25x100 mg, 100x100 mg.
*250 mg:*1x250 mg.
1 g: 1x1 g.

Not all pack sizes and strengths may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

The suspension is prepared as follows:

1. Press firmly on the plastic activator so that the solvent runs down in the lower part of the vial.
2. Shake the pack until the contents have dissolved.
3. Remove the small part of the plastic cap that covers the rubber plug.
4. Disinfect the rubber plug.

   Note! Steps 1-4 must be completed before you continue.

5. Insert the needle vertically through the centre of the rubber plug until the tip of the syringe appears.
6. Invert the pack and draw up the desired dose.

For intravenous infusion the preparation is added to 100-500 ml infusion solution (sodium chloride 9 mg/ml or glucose 55 mg/ml). Up to 3 g Solu-Cortef can be dissolved in 50 ml liquid.

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

6.7. DRUG PRODUCT SPECIFICATION

Submitted with the dossier.

7. REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

Pfizer Pakistan LimitedB-2, S.I.T.E., Karachi

7.1 Manufacturer

Name of Manufacturing site	Address of site	Manufacturing step (if applicable)
Pfizer Manufacturing Belgium NV.	Rijksweg 12, B- 2870 Puurs, Belgium.	Production
Pfizer Pakistan Limited	B-2, S.I.T.E., Karachi	Packaging, Testing & Batch release

8. REGISTRATION / MARKETING AUTHORISATION NUMBER

Solu Cortef 100mg Injection : License no. 000604
Solu Cortef 250mg Injection : License no. 000603
Solu Cortef 500mg Injection : License no. 008253

9. DATE FROM WHICH MARKETING IS AUTHORIZED

Solu Cortef 100mg & 250mg Injection : 5-Aug-1976
Solu Cortef 500mg Injection: 01-Aug-1991

10. DATE OF REVISION OF THE TEXT

Solu-cortef/LPD/PK-02
According to Sweden Approved SmPC dated: 27 September 2023 & approved information in Pakistan

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*