SOLU-CORTEF®

HYDROCORTISONE SODIUM SUCCINATE

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

Reference Market: Belgium

Common Export pack

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solu-Cortef 100 mg Powder and solvent for solution for injection
Solu-Cortef 250 mg Powder and solvent for solution for injection
Solu-Cortef 500 mg Powder and solvent for solution for injection
Solu-Cortef 100 mg Powder for solution for injection
Solu-Cortef 500 mg Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance of Solu-Cortef is hydrocortisone.
This is present in the form of hydrocortisone sodium succinate (133.67 mg, 334.18 mg or 668.35 mg), respectively equivalent to 100 mg, 250 mg or 500 mg of hydrocortisone.

Excipient with known effect: solutions of Solu-Cortef 100 mg, 250 mg and 500 mg powder and solvent for solution for injection, reconstituted in Act-O-Vial, containing 9 mg of benzyl alcohol per ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection;
Powder for solution for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

NON-ENDOCRINE DISORDERS
1. Allergic disorders
   Control of severe or incapacitating allergic conditions not responding to adequate conventional treatments in:
   - Seasonal or perennial allergic rhinitis
   - Serum sickness
   - Bronchial asthma
   - Drug hypersensitivity reactions
   - Contact dermatitis
   - Atopic dermatitis
   - Urticarial transfusion reactions

- Quincke's edema (epinephrine is the drug of first choice)

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

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

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

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

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

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

4.2 Posology and method of administration

Posology
Intravenous injection is the method of first choice for initial treatment of emergency cases. A longer-acting injectable or oral preparation must be considered after this initial period.
The duration of the intravenous administration depends on the dose; it can vary from 30 seconds (100 mg for example) to 10 minutes (500 mg or more, for example).

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

If a treatment with high doses of hydrocortisone needs to be continued for longer than 48 to 72 hours hypernatriaemia can occur. In that case it may be desirable to replace Solu-Cortef by a corticosteroid preparation such as methylprednisolone sodium succinate, which causes little or no sodium retention.

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

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Systemic fungal infections.
Administration of vaccines based on live attenuated virus is contra-indicated in patients. receiving immunosuppressive doses of corticosteroids.

4.4 Special warnings and precautions for use

- Special risk groups:

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

- Children and adolescents: growth retardation can occur in children receiving long-term treatment with glucocorticoids in divided daily doses. Such a regimen is justified only in very severe indications. Growth and development should be closely monitored in infants and children receiving long-term corticosteroid treatment.
- Diabetics: signs of latent diabetes mellitus or increased requirement of insulin or oral hypoglycaemic agents.
- Hypertensive patients: aggravation of arterial hypertension.
- Patients with osteoporosis.
- Patients with active or latent peptic ulcer, diverticulitis, recent intestinal anastomoses, non-specific ulcerative colitis if there is a risk of perforation and abscess or other pyogenic infections.
- Patients with a predisposition for thromboembolism. Thrombosis, including venous thromboembolism, has been reported with corticosteroids. As a result, corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.
- Patients with myasthenia gravis
- Patients with renal insufficiency
- Patients with a history of psychiatric disease: existing emotional instability and psychotic tendencies may be aggravated by corticosteroids. Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, sullen temper, personality disorders and severe depression to frank psychotic manifestations:
- Patients with some infections such as tuberculosis: in active tuberculosis the use of Solu-Cortef should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used in conjunction with appropriate antituberculous chemotherapy. Patients with latent tuberculosis or tuberculin reactivity should be monitored closely during corticotherapy to detect possible reactivation of the disease. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.
- Patients with some viral conditions such as herpes and shingles with ocular symptoms: glucocorticoids should be used with caution in case of ocular herpes simplex because of the risk of corneal perforation.

– Possible effects of corticosteroids include adrenal suppression, decrease in bone mineral density, cataract and glaucoma.
Corticosteroid therapy has been associated with central serous chorioretinopathy, which can lead to retinal detachment.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.
Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used. It is important that the dose of corticosteroid is titrated to the lowest dose at which effective control of symptoms is achieved.

- Cases of epidural lipomatosis have been reported in patients receiving corticosteroids, usually at high doses over the long-term.
- Although brief treatments with high doses of corticosteroids are seldom accompanied by undesirable side-effects, stomach ulcers can occur. Prophylactic use of antacids may be indicated.
- In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting glucocorticosteroids before, during and after the stressful situation is indicated.
- Patients subjected to severe stress after corticosteroid therapy must be kept under close observation for symptoms of adrenocortical insufficiency.
- Glucocorticosteroids 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. Systemic infections involving bacteria, viruses, moulds, protozoa or worms, can be associated with corticosteroid treatment, either alone or in combination with other immunosuppressant substances which have an effect on cell immunity, humoral immunity or neutrophil activity. These infections may be of a moderate or severe nature and in some cases fatal. The number of infections rises with increasing corticoid dosage.
- Hydrocortisone can lead to increase in blood pressure, water- and salt-retention and increased potassium excretion. A sodium-free diet and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
- Administration of attenuated live vaccines is contraindicated in patients being treated with immunosuppressant doses of corticosteroids. Inactivated and biogenetically obtained vaccines may be administered however to these patients. However the response to such vaccines may be diminished or they can even be ineffective. The necessary immunization procedures should be however undertaken in patients being treated with non-immunosuppressant doses of corticosteroids.
- Because rare instances of anaphylactic (e.g. bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration of this product, especially when the patient has a history of allergy to this type of product.
- Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.
- There is an enhanced effect of glucocorticosteroids on patients with hypothyroidism and in those with cirrhosis.
- Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse events and death in paediatric patients, including neonates, characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies (“gasping syndrome”). Although the normal therapeutic doses of this product generally contain quantities of benzyl alcohol substantially lower than those reported in association with gasping syndrome, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Use only if it is necessary and if there are no alternatives possible. If given in high volumes, this product should be used with caution and preferably for short term treatment in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis). Premature babies and babies with a low weight at birth are more likely to develop toxicity. Presentations containing benzyl alcohol must not be given to pre-term or full-term neonates unless strictly necessary. The solution of Solu-Cortef Powder and solvent for solution for injection, reconstituted in Act-O-Vial, contains 9 mg of benzyl alcohol per 1 ml.

- Although no recent studies have been conducted with hydrocortisone, a study with methylprednisolone sodium succinate in septic shock indicated a higher mortality rate in a patient sub-group, namely those persons in whom an elevated serum creatinine level was found (>2%) at the start of the study, or in patients who contracted a secondary infection after commencement of the therapy.
- Although controlled clinical studies have shown that corticosteroids accelerate the resolution of acute exacerbation of multiple sclerosis, there is no evidence whatever that corticosteroids influence the ultimate outcome or the natural course of the disease. The studies have shown that relatively high doses of corticosteroids are necessary for a significant result (see section 4.2 “Posology and method of administration”).
- The occurrence of acute myopathies is reported with the use of high doses of corticosteroids. These occur mostly in patients with neuromuscular transmission disorders (myasthenia gravis for example) or in patients undergoing simultaneous treatment with neuromuscular-inhibiting medication.(pancuronium, for example).
- This acute myopathy can occur anywhere and can affect the eye- and respiratory muscles and can result in quadriparesis. An increase in creatine kinase can be induced. Weeks or even years may pass after the corticosteroid therapy has stopped before a clinical improvement or cure takes place.
- The occurrence of Kaposi sarcoma has been reported in patients treated with corticosteroids. Stopping of the corticosteroid therapy can bring about clinical remission.
- A crisis of pheochromocytoma, which may be fatal, was reported after the administration of systemic corticosteroids. Corticosteroids may only be administered to patients with suspected or identified pheochromocytoma after an appropriate assessment of benefits/risks.
- Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury. A multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.
- Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g. skin tests, thyroid hormone levels).
- The duration of the treatment should in general be kept as short as possible. Medical surveillance is recommended during chronic treatment (see also section 4.2). The discontinuation of a chronic treatment should also occur under medical surveillance (gradual discontinuation, evaluation of the adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.
- Injection into the deltoid muscle should be avoided because of the high incidence of subcutaneous atrophy.
- 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).

4.5 Interaction with other medicinal products and other forms of interaction

- Simultaneous administration of liver enzyme-inducing medicines such as barbiturates, phenylbutazone, phenytoin, carbamazepin or rifampicin can accelerate metabolism and thus diminish the effect of corticosteroids.
- Macrolides such as erythromycin and medicines such as ketoconazole can inhibit the metabolism of corticosteroids. Modification of the corticosteroid dose may be required to prevent overdosing.
- Protease inhibitors (e.g. ritonavir, indinavir) and pharmacokinetic enhancers (e.g. cobicistat) inhibit CYP3A4 activity leading to a decreased hepatic clearance and increased plasma concentration of the corticosteroid. A dose adjustment of the corticosteroid may be required (see section 4.4).
- Glucocorticosteroids can increase the renal clearance of chronic high dose salicylates. This can lead to lowered salicylate levels and to salicylate intoxication when the corticosteroid therapy is stopped.
- Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.
- Corticoids can both reduce and raise the response to anticoagulants. Continuous monitoring of coagulation parameters is consequently necessary.

- Combination of glucocorticosteroids with ulcerogenic drugs (e.g. salicylates and NSAIDs) increases the risk of gastrointestinal complications.
- Combination of glucocorticosteroids with thiazide diuretics increases the risk of glucose intolerance.
- Glucocorticosteroids can increase the requirements for insulin or oral hypoglycemic agents in diabetics.
- Administration of attenuated live vaccines is contraindicated in patients being treated with immunosuppressant doses of corticosteroids. Inactivated and biogenetically obtained vaccines may be administered however to these patients. However the response to such vaccines may be diminished or they can even be ineffective. The necessary immunization procedures may be undertaken in patients being treated with non-immunosuppressant doses of corticosteroids.
- Concomitant administration of glucocorticoids and cholinesterase inhibitors such as neostigmine and pyridostigmine may precipitate myasthenic crisis and the need for respiratory support should be anticipated in this situation.
- The intrinsic mineralocorticoid effect of hydrocortisone results in elevations of blood pressure and may result in increased requirements for antihypertensive agents.
- The toxicity of heart glycosides such as digoxin can increase during concomitant use with corticosteroids because of the intrinsic potassium-depleting effect of hydrocortisone.
- 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.
- If corticosteroids are administered concurrently with potassium-depleting diuretics, potassium should be monitored frequently.
- Concomitant administration of methotrexate and corticosteroids can have synergistic effects on the disease state and permit reduction in corticosteroid dose.
- Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. Prolonged coadministration of these agents may increase the risk and/or severity of myopathy resulting in prolonged paralysis following discontinuation of the neuromuscular blocking agent
- Corticosteroids increase the number of beta receptors and so may increase sensitivity to β_2-receptor agonists.
- Post-marketing surveillance reports indicate that the risk of tendon rupture may be increased in patients receiving fluoroquinolones and corticosteroids, especially in the elderly.

4.6 Fertility, pregnancy and lactation

Pregnancy

Corticosteroids readily cross the placenta. One retrospective study revealed an increased incidence in low birth weight in infants whose mothers had received corticosteroids.

Though neonatal adrenocortical insufficiency is rare in infants who were exposed in utero to corticosteroids, infants born of mothers who have received substantial doses of glucocorticoids during pregnancy, should be carefully observed and evaluated for signs of adrenocortical insufficiency.

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

In case of labour and delivery no effects are known.

The following precaution applies only to presentations containing benzyl alcohol: benzyl alcohol may cross the placenta (see section 4.4 "Special warnings and precautions").

Some animal studies have shown that corticosteroids when administered during pregnancy at high doses, may cause fetal malformations (see section 5.3).

Since safety in pregnancy has not been adequately demonstrated, this medicine should not be used during pregnancy unless it is strictly necessary.

Breast-feeding
Corticosteroids are excreted in breast milk.
There is no evidence that corticosteroids are carcinogenic, mutagenic or impair fertility.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Side effects	
System Organ Class	**Frequency unknown (cannot be estimated from the available data)**
Infections and infestations	Masking of infections; Opportunistic infections, ranging from mild to fatal, due to any pathogen, and at any location in the body; Infection (activation of, including reactivation of tuberculosis).
Benign, malignant and unspecified tumours (including cysts and polyps)	Kaposi's sarcoma has been reported in patients treated with corticosteroids.
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Hypersensitivity reactions, including anaphylaxis and anaphylactic reactions (bronchospasm, laryngeal oedema, urticaria); Potential inhibition of skin test reactions
Endocrine disorders	Cushing's syndrome; Inhibition of the pituitary-adrenal axis.
Metabolic and nutritional disorders	Sodium retention; Fluid retention; Hypokalaemic alkalosis; Impaired glucose tolerance; Reactivation of latent diabetes mellitus.
Psychiatric disorders	Psychiatric disorders or psychotic manifestations (euphoria, insomnia, changeable mood, changes in personality, severe depression, worsening of emotional instability, worsening of pre-existing psychotic behaviour).
Nervous system disorders	Increased intracranial pressure; Benign intracranial hypertension;

Side effects	
System Organ Class	**Frequency unknown (cannot be estimated from the available data)**
	Convulsions; Dizziness; Epidural lipomatosis.
Ocular disorders	Prolonged use of glucocorticoids can lead to posterior subcapsular cataracts, glaucoma with potential damage to the ocular nerves, and may promote the development of secondary fungal or viral eye infections; Glucocorticoids should be administered with caution in cases of ocular herpes simplex, due to the possibility of corneal perforation; Exophthalmos; Central serous chorioretinopathy ; Vision, blurred (see also section 4.4).
Cardiac disorders	Congestive heart failure (in susceptible patients)
Vascular disorders	Thrombosis, hypertension
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, Gasping syndrome (respiratory disorder characterized by a persistent gasping for breath).
Gastrointestinal disorders	Peptic ulcer (potentially with perforation and haemorrhage); Gastric haemorrhage; Pancreatitis; Oesophagitis; Intestinal perforation.
Skin and subcutaneous tissue disorders	Petechiae; Bruising; Atrophy of the skin; Thin and fragile skin; Facial erythema; Increased sweating; Acne; Stretch marks.
Musculoskeletal and connective tissue disorders	Steroidal myopathy; Muscular weakness; Osteonecrosis; Aseptic necrosis; Osteoporosis; Pathological fractures; Inhibition of growth in children.
Reproductive system and breast disorders	Irregular menstruation
General disorders and anomalies at the site of administration	Slowed healing of wounds
Investigations	Increased intraocular pressure; Decreased glucose tolerance; Increase in requirement for insulin or oral hypoglycaemic agents) in diabetic patients; Decreased serum potassium; Negative nitrogen balance (due to protein catabolism); Increase calcium excretion; There may be a transient and moderate increase in ALT, ALS and blood alkaline phosphatase, with no apparent clinical syndromes.
Lesions, toxicity and procedural complications	Vertebral compression fractures; Tendon tears (in particular, tearing of the Achilles tendon).

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

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

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 according to their local country requirements.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticoids, ATC code: H02AB09

Glucocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin), and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the numerous effects of glucocorticoids after systemic use. Glucocorticoids not only have an important influence on inflammatory and immune processes, but also affect the carbohydrate, protein and fat metabolism. They also act on the cardiovascular system, the skeletal muscles and the central nervous system.

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

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

5.2 Pharmacokinetic properties

After intramuscular administration of Solu-Cortef the peak serum levels are reached about 30 - 60 minutes after injection. The serum protein binding amounts to about 40 to 90 %. By far the greater part is eliminated after binding with a globulin (transcortin) and only a small quantity is bound to albumin. The free unbound fraction of the hormone determines the biological activity of the hormone while the bound fraction serves as reserve.
Hydrocortisone is metabolised principally in the liver. 22 - 30 % of intravenous and intramuscular administered doses are excreted via the urine within 24 hours.
As elimination from the bloodstream is practically complete after about 12 hours intravenous and intramuscular injections should be repeated every 4-6 hours if maintenance of a high blood-level is required.

5.3 Preclinical safety data

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

Carcinogenicity:
Due to the indication of this medicinal product for treatments of short duration only, long-term studies to evaluate its carcinogenic potential in animals have not been conducted.

Mutagenicity:
No potential for genetic or chromosomal mutation was identified in limited studies carried out in bacterial and mammalian cells.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Solu-Cortef 100 mg, 250 mg, 500 mg, powder and solvent for solution for injection:

- Powder for solution for injection (lower compartment of Act-O-Vial): Anhydrous Monobasic Sodium Phosphate Monohydrate - Dibasic Sodium Phosphate Dried.
- Solvent for solution for injection (upper compartment of Act-O-Vial): Benzyl Alcohol *- Water for Injections.

* See also section "4.4 Special warnings and precautions for use" for Benzyl Alcohol.

- Solu-Cortef 100 mg, 500 mg, powder for solution for injection: Anhydrous Monobasic Sodium Phosphate Monohydrate - Dibasic Sodium Phosphate Dried.

6.2 Incompatibilities

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

6.3 Shelf life

Unreconstituted product:
Do not use Solu cortef after the expiry date which is stated on the carton label after "EXP":. The expiry date refers to the last day of that month**.**
Solution reconstitued with Act-O-Vial: the solution is to be used immediately.

6.4 Special precautions for storage

Unreconstituted product:
Solu-Cortef 100 mg powder and solvent for solution for injection (Act-O-Vial bottle): store below 30 °C .

Solu-Cortef 250 mg, 500 mg, powder and solvent for solution for injection (Act-O-Vial bottle) and Solu-Cortef 100 mg, 500 mg, powder for solution for injection (bottle): store below 30 °C .

Reconstitued solution:
- Act-O-Vial: do not freeze and protect from light.
  For storage conditions after reconstitution of the medicinal product, see section 6.3.
-Plain Vial 100 mg sterile powder (bottle): Store at 2-8°C and use within 72 hours"

6.5 Nature and contents of container

Pack sizes:Solu-Cortef 100 mg and 250mg, powder and solvent for solution for injection:
1 Act-O-Vial (2 ml)*
Hospital pack sizes:
Solu-Cortef 500 mg, powder and solvent for solution for injection:
1 Act-O-Vial (4 ml)
Solu-Cortef 100 mg, 500mg, powder for solution for injection: 1 vial
* Act-O-Vial: a 2 compartments vial which allows a simple and instant preparation of the sterile solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Directions for use of the Act-O-Vial
1. Press down the plastic cap to force solvent into the lower compartment.
2. Gently agitate to complete dissolving.
3. Remove plastic protective strip.
4. Sterilize the rubber stopper.
5. Insert needle squarely through center of stopper until tip is just visible in the lower compartment. Turn the vial and draw up the required dose.

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

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

The 250 mg solution may be added to 250 - 1000 ml and the 500 mg solution to 500 - 1000 ml of the same diluents.

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

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

The osmolar values are
0.36 osmolar for the 100 mg AOV
0.57 osmolar for the 250 mg AOV
0.57 osmolar for the 500 mg AOV
(0.28 osmolar = isotonic saline solution).
Keep out of sight and reach of children.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer S.A., 17 Boulevard de la Plaine, 1050 Bruxelles, Belgium.

MANUFACUTRED, PACKED & RELEASED BY

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8. DATE OF REVISION OF THE TEXT

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