SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

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

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

COMPOSITION:

SOLU-CORTEF 100 mg Act-O-Vial is a two compartment vial containing per 2 ml when mixed, hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone, 0,9 % m/v benzyl alcohol, and water for injection.

SOLU-CORTEF 500 mg Act-O-Vial is a two compartment vial containing per 4 ml when mixed, hydrocortisone sodium succinate equivalent to 500 mg hydrocortisone, 0,9 % m/v benzyl alcohol, and water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 21.5 Corticosteroids

PHARMACOLOGICAL ACTION:

SOLU-CORTEF 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. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours. This preparation is also rapidly

absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injections.

INDICATIONS:

Sterile SOLU-CORTEF is indicated in situations requiring a rapid and intense hormonal effect.

Acute Adrenocortical Insufficiency - This syndrome may be induced by severe stress (e.g. surgery, trauma, or infection) in patients with Addison's disease, panhypopituitarism, or latent adrenocortical insufficiency due to corticosteroid therapy. Patients in these categories should be prepared for elective surgery with prophylactic doses of cortisone or hydrocortisone. Should evidence of adrenal insufficiency develop despite preparation, SOLU-CORTEF should be administered promptly to support the patient. Cases in this group which require emergency surgery that does not permit prophylactic preparation with steroids should receive this product intravenously before the operative procedure and at the same time be started on intramuscular cortisone or hydrocortisone. The latter should be continued for an appropriate interval into the post-operative period.

Bilateral Adrenalectomy - Patients who are to undergo this procedure should be prepared with intramuscular injections of cortisone and hydrocortisone before surgery. Hydrocortisone sodium succinate should be given intravenously immediately prior to the operation and at appropriate intervals to support the patient through the period of maximum stress. Steroid dosage should be tapered following the procedure and the patient eventually transferred to oral replacement therapy.

Severe Shock - In severe shock adjunctive use of intravenous SOLU-CORTEF may aid in achieving haemodynamic restoration. Corticoid therapy should not replace standard methods of combating shock, but present evidence indicates that concurrent use of large doses of corticoids with other measures may improve survival rates.

Acute Hypersensitivity Reactions - In status asthmaticus, and allergic drug anaphylactic reactions, epinephrine or other vasopressor substances should be given before or along with hydrocortisone sodium succinate.

Overwhelming Infections with Severe Toxicity - In patients moribund from overwhelming infections for which specific antibiotic therapy is available, intensive SOLU-CORTEF therapy may permit survival until the antibiotic has time to take effect. Necessary procedures for the establishment of a bacterial diagnosis should be carried out and intensive antibiotic treatment begun on the basis of the proven or probable etiology before steroid therapy is started. In the presence of infection, this product should be administered for the shortest time compatible with adequate clinical response and must be discontinued before the antibiotics by at least 3 days. In the case of surgical infections, definitive surgical therapy should be scheduled as promptly as the patient's condition permits. Clinical improvement resulting from steroid therapy must not be cause to defer surgical treatment.

Systemic Lupus Erythematosus in Relapse - In this condition intravenous administration of SOLU-CORTEF is of value in initiating therapy. Oral therapy with appropriate doses of adrenal steroids should be employed as soon as clinical improvement occurs.

Aspiration Pneumonitis - Intravenous administration of hydrocortisone has been found to be beneficial in the management of pneumonitis produced by aspiration of vomitus. The beneficial effect appears to be due to inhibition of the inflammatory response to chemical irritation.

Aspiration of vomitus usually occurs during inhalation anaesthesia. Obstetrical patients appear to be particularly liable. Such aspiration may be followed by the development of a clinical syndrome (Mendelson's syndrome) within two to five hours, consisting of cyanosis, dyspnoea, tachycardia and shock. Physical signs may include those due to shock and those due to pulmonary oedema and bronchoconstriction. X-ray of the chest may show soft patchy areas of consolidation throughout the lung fields. Deterioration of the patient's condition with a fatal termination may occur rapidly.

Treatment consists of the immediate institution of all measures necessary to oxygenate the patient and clear the airway. These include discontinuance of the general anaesthetic, aspiration of vomitus from the pharynx and larynx, clearance of the larynx and bronchial tree under direct laryngoscopy and bronchoscopy, and positioning of the patient to minimise the possibility of further aspiration. SOLU-CORTEF 100 mg should be given immediately and repeated every six to eight hours for two or three days or until the chest is clear. The same dosage may be employed in children. Intravenous administration of the initial dose is recommended. If desired, subsequent doses may be given by intravenous infusion or intramuscularly. Full doses of a broad range antibiotic or combination of antibiotics should be given to prevent the development of secondary infection.

If brochoconstriction is prominent, intravenous administration of a brochodilator drug (aminophylline, isoproterenol) may be beneficial. Expectorant cough mixtures may aid in the removal of bronchial secretions.

CONTRAINDICATIONS:

Except when used for short-term or emergency therapy as in acute sensitivity reactions, SOLU-CORTEF, like any corticoid, is usually considered to be absolutely contraindicated in patients with herpes simplex keratitis, acute psychoses, and in patients with latent, healed or active tuberculosis. However, concurrent administration of corticoids with antituberculous agents may be life-saving in certain cases of pulmonary or meningeal tuberculosis. Corticosteroids should not be given unless the tubercle bacilli have been shown to be sensitive to the antituberculous agents being employed. The following conditions are considered to be relative contraindications: active or latent peptic ulcer, Cushing's syndrome, diverticulitis, fresh intestinal anastomoses, osteoporosis, renal insufficiency, thromboembolic tendencies, psychotic tendencies, diabetes mellitus, hypertension, local or systemic infections including vaccinia and varicella, as well as fungal diseases and other exanthematous diseases.

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

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

WARNINGS and SPECIAL PRECAUTIONS:

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

Because of its inhibitory effect on fibroplasia, hydrocortisone may mask the signs of infection and enhance dissemination of the infecting organism. Hence, all patients receiving hydrocortisone should be observed for evidence of intercurrent infection. Should infection occur, it must be brought under control by use of appropriate antibacterial measures.

If possible, abrupt cessation of corticosteroid therapy should be avoided because of the danger of superimposed adrenocorticoid insufficiency on the infectious process.

Prolonged hormone therapy usually causes a reduction in the activity and size of the adrenal cortex. Relative adrenocortical insufficiency upon discontinuation of therapy may be avoided by gradual reduction of dosage. However, a potentially critical degree of insufficiency may persist asymptomatically for some time even after gradual discontinuation of adrenocortical steroids. Therefore, if a patient is subjected to significant stress, such as surgery, trauma or severe illness while being treated or within one year (occasionally up to two years) after treatment has been terminated, hormone therapy should be augmented or reinstituted and continued for the duration of stress and immediately following it. Since mineralocorticoid secretion may be impaired, salt and/or desoxycorticosterone should be administered conjunctively. It is preferable to use a soluble hormone preparation in the immediate pre-operative and post-operative periods.

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

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention and increased potassium and calcium excretion. Dietary salt restriction and potassium supplementation may be necessary. Like other glucocorticoids, hydrocortisone may aggravate diabetes mellitus so that higher insulin dosage may become necessary or manifestation of latent diabetes mellitus may be precipitated. The use of steroids in myasthenia gravis may aggravate myasthenic symptoms and should therefore be given with proper precautions.

Weakness of voluntary musculature has been reported following systemic administration of any of the anti-inflammatory steroids. In some instances this has been attributed to hypopotassemia. This effect should be kept in mind and periodic determinations of serum potassium performed in patients receiving any corticoid for prolonged periods. Current investigators indicate that weakness of the voluntary musculature in patients receiving corticoids may occur in the presence of normal serum potassium levels and may be due to a disturbance in muscle metabolism. Patients who developed severe myopathy received corticoids in substantial doses for prolonged periods.

Presently available data indicate that severe myopathy, complicating steroid therapy, occurs more frequently in those patients receiving steroids containing the 9-alpha-fluorinated configuration. In some instances improvement in steroid-induced myopathy has been noted

following withdrawal of the fluorinated steroid and institution of therapy with cortisone, hydrocortisone or prednisteroid.

Retardation of linear growth has been noted in children receiving corticoids for 6 months or longer, the retardation being roughly proportional to the dose. Following cessation of therapy, the growth rate may be accelerated. For this reason, the growth of children receiving prolonged steroid therapy should be observed carefully. If growth is retarded, the dose should be reduced sufficiently to permit recovery before epiphyseal closure. Anaphylactic and other reactions have occasionally been reported following parenteral SOLU-CORTEF therapy. Physicians using the drug should be prepared to deal with such a possibility.

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

Long-term adrenocorticoid therapy may evoke a rise in hyperacidity or peptic ulcer, therefore, as a prophylactic measure, an ulcer regimen and the administration of an antacid are highly recommended. X-rays should be taken in peptic ulcer patients complaining of gastric distress, and whether or not changes are noted, an ulcer regimen is recommended.

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

Continued supervision of the patient after cessation of hydrocortisone sodium succinate therapy is essential, since there may be a sudden re-appearance of severe manifestations of the disease for which the patient was treated.

DOSAGE AND DIRECTIONS FOR USE:

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

In treating severe shock, there is a tendency in current medical practice to use massive (pharmacologic) doses of corticosteroids. The following are SOLU-CORTEF doses suggested by various authors:

AUTHOR	DOSE	REPEAT
Melby	0,5 gram	Every 4 to 6 hours
Oaks	1-2 grams	Every 2 to 6 hours
Melnick	1 gram	50 mg/kg every 24 hours
Wilson	50 mg/kg	50 mg/kg every 24 hours
Dietzman	50 mg/kg	Within four hours if needed.

Therapy is initiated by administering SOLU-CORTEF intravenously over a period of one to several minutes. In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized - usually not beyond 48 to 72 hours. Although adverse effects

associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

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

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

This dose may be repeated at intervals of 1, 3, 6 and 10 hours, as indicated by the patient's response and clinical condition. While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient, than by age or body mass, but should not be less than 25 mg daily.

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

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

Directions for using the Act-O-Vial system:

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

Further dilution is not necessary for intravenous or intramuscular injection.

For intravenous infusion, first prepare the solution as described above. The solution may then be added to 100 ml to 1000 ml of 5 % dextrose in water (or isotonic saline solution or 5 % dextrose in isotonic saline solution if patient is not on sodium restriction).

Important:

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

SIDE EFFECTS:

Adverse reactions associated with use of corticoids include: Cushing's syndrome, moon facies, supraclavicular fat pads, hirsutism, striae and acne, relative adrenocortical insufficiency particularly in time of stress due to trauma, surgery or severe illness, protein catabolism with negative nitrogen balance, electrolyte imbalance, alteration of glucose metabolism with aggravation of diabetes mellitus including hyperglycaemia and glycosuria; osteoporosis reversible only with difficulty; spontaneous fractures; aseptic necrosis of the hip and humerus;

activation and complication of peptic ulcer including perforation and haemorrhage; aggravation or masking of infection; increased blood pressure; convulsions; petechiae and purpura; menstrual irregularities including amenorrhoea, spotting or prolonged bleeding; insomnia; psychic disturbances especially abnormal euphoria; nervousness; posterior subcapsular cataracts occasionally requiring extraction; increased intra-ocular tension; increased intracranial pressure with papilloedema (pseudotumor cerebri); pancreatitis; necrotizing angiitis; suppression of growth in children; facial erythema; ulcerative oesophagitis; sweating; vertigo; weakness; myopathy; headache; exophthalmos.

Subcutaneous and cutaneous atrophy; post injection flare, sterile abscess, hyper- and hypopigmentation have been associated with injected corticoids.

When adverse reactions occur, they are usually reversible and disappear when the hormone is discontinued.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment should be symptomatic and supportive.

IDENTIFICATION:

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

PRESENTATION:

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

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

STORAGE INSTRUCTIONS:

Store unreconstituted product at room temperature (15 ° - 30 °C). While solutions, when reconstituted as directed, are relatively stable at room temperature (15 ° - 30 °C) and below, if protected from light, unused solutions should be discarded after 3 days.

Keep out of reach of children.

REGISTRATION NUMBERS:

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

SOLU-CORTEF 500 mg: G/21.5/201

BACTERIOSTATIC WATER FOR INJECTION: H/34/60

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Limited

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South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

26 August 1992

BOTSWANA: S2
Solu- Cortef 100 mg - Reg. No.: B9312150
Solu- Cortef 500 mg - Reg. No.: B9312155

NAMIBIA: S2
Solu- Cortef 500 mg- Reg. No.: 90/20.1.5/001358