

# HYDROCORTISONE (as SODIUM SUCCINATE) 100 mg FOR INJECTION Sterile Powder

## COMPOSITION

White, freeze-dried powder of hydrocortisone sodium succinate, equivalent to 100 mg hydrocortisone, supplied in rubber-capped vials.

## CLINICAL PARTICULARS

### Therapeutic indications

Anti-inflammatory agent

### Pharmacotherapeutic group

Glucocorticoids, ATC-Code: H02AB

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

#### Endocrine disorders:

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogues may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogues are used).

Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Congenital adrenal hyperplasia.

Nonsuppurative thyroiditis.

Hypercalcemia associated with cancer.

#### Rheumatic disorders:

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: post-traumatic osteoarthritis; synovitis or osteoarthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); acute and subacute bursitis; epicondylitis; acute nonspecific tenosynovitis; acute gouty arthritis; psoriatic arthritis; ankylosing spondylitis.

#### Collagen diseases:

During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; acute rheumatic carditis; systemic dermatomyositis (polymyositis).

#### Dermatological disease:

Pemphigus; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; bullous dermatitis herpetiformis; severe seborrheic dermatitis; severe psoriasis; mucosis fungoides.

#### Allergic states:

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; seasonal or perennial allergic rhinitis; drug hypersensitivity reaction; urticarial transfusion reactions; acute noninfectious laryngeal edema (epinephrine is the drug of first choice); anaphylactic reactions.

#### Ophthalmic diseases:

Severe acute and chronic allergic and inflammatory processes involving the eye, such as: herpes zoster ophthalmicus; iritis, iridocyclitis; chorioretinitis; diffuse posterior uveitis and chroiditis; optic neuritis; sympathetic ophthalmia; anterior segment inflammation; allergic conjunctivitis; allergic corneal marginal ulcers; keratitis.

#### Gastrointestinal diseases:

To tide the patient over a critical period of the disease in: ulcerative colitis (systemic therapy); regional enteritis (systemic therapy); Crohn's disease.

#### Respiratory diseases:

Symptomatic sarcoidosis; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculosis chemotherapy; Loeffler syndrome not manageable by other means; aspiration pneumonitis.

#### Hematologic disorders:

Acquired (autoimmune) hemolytic anemia; idiopathic thrombocytopenia purpura in adults (IV only; IM administration is contraindicated); erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia; secondary thrombocytopenia in adults.

#### Neoplastic diseases:

For palliative management of: leukemias and lymphoma in adults; acute leukemia of childhood.

#### Edematous states:

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

#### Medical emergencies:

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION is indicated in the treatment of:

- Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenocortical insufficiency may be present.
- Acute allergic disorders (status asthmaticus, anaphylactic reactions, insect stings, etc.) following epinephrine. Although there are no well controlled (double blind, placebo) clinical trials, data from experimental animal models indicate that corticosteroids may be useful in hemorrhagic, traumatic and surgical shock in which standard therapy (e.g. fluid replacement, etc.) has not been effective (see Special precautions).

## Miscellaneous:

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculosis chemotherapy.

Trichinosis with neurologic or myocardial involvement.

## Dosage and method of administration

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION 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 employ a longer-acting injectable preparation or an oral preparation.

Dosages usually range from 100 mg to 500 mg depending on 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.

In general, high dose corticosteroid therapy should be continued only till the patient's condition has stabilised - usually between 48–72 hours. If hydrocortisone therapy must be continued beyond 48 to 72 hours hypernatremia may occur.

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

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

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

### Elderly patients:

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION is primarily used in acute short-term conditions. There is no information to suggest that a change in dosage is warranted in the elderly. However, treatment in elderly patients should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroid in elderly patients and close clinical supervision is required (see Special warnings and special precautions for use).

### Children:

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 the age or body weight but should not be less than 25 mg daily (see Special warnings and special precautions for use).

### Preparation of solutions:

For intravenous or intramuscular injection prepare the solution aseptically by adding not more than 2 ml sterile water for injections to the vial containing 100 mg. Shake and withdraw for use.

For intravenous infusion, prepare a primary solution as above and then add 100–1000 ml (not less than 100 ml) of 5% dextrose in water, or isotonic saline 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 7.0–8.0.

## Contraindications

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION is contraindicated where there is known hypersensitivity to components and in systemic fungal infection unless specific anti-infective therapy is employed.

Administration of live or live-attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

## Special warnings and special precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the minimum period.

Frequent patient observation is required to appropriately titrate the dose vs. disease activity (see Dosage and method of administration).

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 adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any intercurrent illness, trauma or surgical procedures will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy, they may need to be temporary re-introduced. Patients should carry "Steroid Treatment" cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Corticosteroids 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.

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 immunoglobulin (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 care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Live vaccines should not be given to individuals

with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

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

Rarely, anaphylactoid reactions have been reported following parenteral HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION therapy. Physicians using the drug should be prepared to deal with such a possibility. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

Care should be taken with patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see Adverse effects).

#### **Special precautions:**

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary: osteoporosis (post-menopausal females are particularly at risk); hypertension or congestive heart failure; existing or previous history of severe affective disorders (especially previous steroid psychosis); diabetes mellitus (or a family history of diabetes).

History of tuberculosis; glaucoma (or a family history of glaucoma); previous corticosteroid-induced myopathy; liver failure or cirrhosis; renal insufficiency; epilepsy, peptic ulceration; fresh intestinal anastomoses; predisposition to thrombophlebitis; abscess or other pyogenic infections; ulcerative colitis; diverticulitis; myasthenia gravis; ocular herpes simplex for fear of corneal perforation; hypothyroidism.

#### **Use in children:**

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. The use of steroids should be restricted to the most serious indications.

#### **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.

#### **Interaction with other medications and other forms of interaction**

Convulsions have been reported with concurrent use of corticosteroids and cyclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur.

Drugs that induce hepatic enzymes, such as rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Drugs such as erythromycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance.

Steroids may reduce the effects of anticholinesterases in myasthenia gravis. The desired effects of hypoglycaemic agents (including insulin), antihypertensives and diuretics are antagonised by corticosteroids and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothermia.

Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.

#### **Pregnancy and lactation**

Corticosteroids cross the placenta. There may be a very small risk of cleft palate and intra-uterine growth retardation in the fetus; there is evidence of harmful effects on pregnancy in animals. 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.

Because prednisolone is excreted in breast milk, it is reasonable to assume that all corticosteroids are. Infants of mothers taking pharmacological doses of steroids should be monitored carefully for signs of adrenal suppression.

#### **Effects on ability to drive and use machines**

None stated.

#### **Adverse effects**

Since HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION is normally employed on a short-term basis it is unlikely that side-effects will occur; however, the possibility of side-effects attributable to corticosteroid therapy should be recognised (see Special warnings and special precautions for use). Such side-effects include:

**Parenteral corticosteroid therapy:** Anaphylactoid reaction, e.g. bronchospasm, hypopigmentation or hyperpigmentation, subcutaneous and cutaneous atrophy, sterile abscess, laryngeal oedema and urticaria.

**Gastrointestinal:** Dyspepsia, peptic ulceration with perforation and haemorrhage, abdominal distension, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis, perforation of bowel.

Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

**Anti-inflammatory and immunosuppressive effects:** Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, may suppress reactions to skin tests, recurrence of dormant tuberculosis (see Special warnings and special precautions for use).

**Musculoskeletal:** Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, aseptic necrosis, muscle weakness.

**Fluid and electrolyte disturbance:** Sodium and water retention, potassium loss, hypertension, hypokalaemic alkalosis, congestive heart failure in susceptible patients.

**Dermatological:** Impaired healing, petechiae and ecchymosis, skin atrophy, bruising, striae, increased sweating, telangiectasia, acne.

**Endocrine/metabolic:** Suppression of the hypothalamo-pituitary-adrenal axis; growth suppression in infancy, childhood and adolescence; menstrual irregularity and amenorrhoea, Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative nitrogen and calcium balance, increased appetite.

**Neuropsychiatric:** Euphoria, psychological dependence, mood swings, depression, personality changes, insomnia, convulsions, increased intra-cranial pressure with papilloedema in children (pseudo-tumour cerebri), usually after treatment withdrawal. Psychosis, aggravation of schizophrenia seizures.

**Ophthalmic:** Increased intra-ocular pressure, glaucoma, papilloedema, cataracts with possible damage to the optic nerve, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, exophthalmos.

**General:** Leucocytosis, hypersensitivity reactions including anaphylaxis, thromboembolism, nausea, malaise.

**Withdrawal symptoms:** Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see Special warnings and special precautions for use). A 'withdrawal syndrome' may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

#### **Overdosage**

There is no clinical syndrome of acute overdosage with HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION. Hydrocortisone is dialysable.

#### **FURTHER INFORMATION**

HYDROCORTISONE SODIUM SUCCINATE FOR INJECTION has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biological activity. 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, injection 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 injection.

#### **PHARMACEUTICAL PRECAUTIONS**

##### **List of excipients**

Disodium Hydrogen Phosphate (anhydrous)

##### **Incompatibilities**

No diluents, other than those referred to, are recommended.

##### **Shelf life**

2 years. Store below 25°C. Protect from light.

After dilution for IV or IM injection (see Dosage and method of administration), stable at room temperature for 24 hours and for 48 hours under refrigeration. For IV infusion in Sodium Chloride Solution 0.9%, Dextrose Solution 5%, and Dextrose Solution 5% with Sodium Chloride Solution 0.45% over 24 hours.

##### **Presentations**

Pack of 100 vials.

##### **Special precautions for disposal and other handling**

Unused solution should be discarded immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

#### **MANUFACTURER**

Panpharma - Beignon, France

#### **LICENSE HOLDER**

Pharmalogic Ltd., P.O.B. 3838, Petah-Tikva 49130

#### **Registration number:**

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