Package Insert

Sterile Powder

Pr

Hydrocortisone Sodium Succinate for Injection

BP

Glucocorticoid

ACTION AND CLINICAL PHARMACOLOGY

Hydrocortisone sodium succinate is a corticosteroid, and a highly water soluble ester derivative of hydrocortisone. It has the same metabolic and anti inflammatory actions as hydrocortisone. High blood levels of hydrocortisone are attained following intravenous injection.

Pharmacological effects have been noted within minutes and persist for variable periods of time. Excretion occurs primarily within 12 hours so that if high blood levels need to be maintained hydrocortisone injections are to be repeated every 4 to 6 hours. The intravenous route is preferred for initial emergency treatment.

INDICATIONS AND CLINICAL USE

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

1. Endocrine Disorders

Congenital adrenal hyperplasia; Hypercalcemia associated with cancer; Primary or secondary adrenocortical insufficiency or acute adrenocortical insufficiency (hydrocortisone is the drug of choice - it may also be used to supplement synthetic analogs); Patients with known adrenal insufficiency or when adrenocortical reserve is doubtful; Preoperatively; Serious trauma or illness; Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected; Nonsuppurative thyroiditis.

2. Allergic States

Acute non infectious laryngeal oedema (though epinephrine is the drug of first choice);
Control of severe or incapacitating allergic reactions:

Drug hypersensitivity reactions; Serum sickness; Seasonal or perennial allergic rhinitis; Urticarial transfusion reactions.

3. Respiratory Diseases

Aspiration pneumonitis; Berylliosis; Bronchial asthma; Concurrently with appropriate antituberculous chemotherapy in fulminating or disseminated pulmonary tuberculosis; Loeffler's syndrome not manageable by other means; Symptomatic sarcoidosis.

4. Dermatologic Diseases

Atopic dermatitis; Bullous dermatitis herpetiformis; Contact dermatitis; Exfoliative dermatitis; Mycosis fungoides; Pemphigus; Severe erythema multiforme (Stevens-Johnson syndrome); Severe seborrheic dermatitis; Severe psoriasis.

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5. Rheumatic Disorders

As adjunctive therapy for short-term administration during an acute episode or exacerbation of:
Acute and sub acute bursitis; Acute nonspecific tenosynovitis; Acute gouty arthritis; Ankylosing spondylitis; Epicondylitis; Psoriatic arthritis; Post-traumatic osteoarthritis; Rheumatoid arthritis, including juvenile rheumatoid arthritis Synovotis or osteoarthritis.

6. Neoplastic Diseases

For palliative management of:
Acute leukemia of childhood; Leukemias and lymphomas in adults.

7. Gastrointestinal Diseases

To alleviate the exacerbation of:
Ulcerative colitis; Regional enteritis.

8. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:
Acute rheumatic carditis; Systemic lupus erythematosus; Systemic dermatomyositis (Polymyositis).

9. Oedematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome (idiopathic or that due to lupus erythematosus or in the absence of uremia).

10. Ophthalmic Diseases

Severe allergic and inflammatory reactions, both acute and chronic, involving the eye, such as:
Anterior segment inflammation; Allergic conjunctivitis; Allergic corneal marginal ulcers; Chorioretinitis; Diffuse posterior uveitis and choroiditis; Herpes zoster opthalmicus; Iritis, iridocyclitis; Keratitis; Optic neuritis; Sympathetic ophthalmia.

11. Haematological Disorders

Acquire (autoimmune) hemolytic anemia; Congenial (erythoid) hypoplastic anemia; Erythroblastopenia (RBC anemia); Idiopathic thrombocytopenia purpura in adults (IV only; IM administration is contraindicated); Secondary thrombocytopenia in adults.

12. Medical Emergencies

1) Acute allergic disorders (status asthmaticus, anaphylactic reactions) following epinephrine;
2) Shock secondary to adrenocortical insufficiency or shock unresponsive to conventional therapy when adrenal cortical insufficiency may be present.

Corticosteroids may be useful in haemorrhage, traumatic and surgical shock in which standard therapy (e.g. fluid replacement, etc.) has not been effective. **See Warning statement**.

13. Others

Tuberculosis meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculosis chemotherapy, Trichinosis with neurologic or mycocardial involvement.

The respiratory distress syndrome in neonates may be prevented by antenatal administration of

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glucocorticoid would probably be used.

CONTRAINDICATIONS

Hypersensitivity to hydrocortisone sodium succinate or phosphate.
Systemic fungal infections.
Herpes simplex keratitis, acute psychoses, and tuberculosis except in emergency situations.

WARNINGS

Continued supervision of the patient after cessation of hydrocortisone is essential, since there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated.

In rare instances, anaphylactoid reactions such as bronchospasm have occurred in patients receiving parenteral corticosteroid therapy. Take appropriate precautionary measures prior to administration, especially when the patient has a history of allergy to any drug.

Pronounced pulmonary oedema or cardiac enlargement and congestive heart failure can occur, especially in patients with previously diminished cardiac reserve. Occasionally, signs and symptoms of salt and water retention may appear quite suddenly. There may be some elevation of arterial blood pressure, peripheral oedema, or ascites if therapy is continued despite early signs of fluid retention.

Infection may be masked while a patient is being treated with adrenocortical hormones or infections may appear during their use. Appropriate anti-infective therapy should be initiated. as necessary and hydrocortisone treatment should be discontinued. Avoid abrupt cessation of hormonal therapy if possible because of the danger of superimposing adrenocortical insufficiency on the infectious process.

Hydrocortisone can cause elevation of blood pressure, salt retention, oedema and potassium and calcium excretion. Dietary salt restriction and potassium supplementation may be required.

Patients under corticosteroid treatment should not be vaccinated against smallpox. Conversely, patients with vaccinia should not receive corticosteroid therapy. Patients receiving corticosteroids should not be subject to immunizing procedures.

Patients should be monitored for suppression of adrenal function while on repeated hydrocortisone administration.

If reconstituted with Bacteriostatic Water for Injection containing benzyl alcohol, then it should be noted that benzyl alcohol in such a product has been reported to be associated with a fatal "gasping syndrome" in premature infants.

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculosis 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.

In treatment for septic shock, studies with the related corticosteroid, methylprednisolone, suggest that increased mortality may occur in some groups of patients who are at higher risk, such as those with elevated creatinine greater than 2.0 mg% or with secondary infections.

Pregnancy: Use of adrenocortical hormones in pregnancy should be limited to conditions serious enough to warrant such treatment, so that possible risk to the fetus may be justified by the expected benefit to the mother. Infants of mothers who have received adrenocortical hormones during pregnancy should be observed closely after delivery for signs of hypoadrenalism, and corrective

hormone therapy and other appropriate measures instituted if such signs are seen.

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.

Lactation: Corticosteroids are excreted in milk.

PRECAUTIONS

Growth and development of children on prolonged corticoid therapy should be carefully observed. Such a regimen should be restricted to the most severe indications.

Exercise caution when steroids are used in nonspecific ulcerative colitis and myasthenia gravis.

Corticosteroids may suppress reaction to skin tests.

Psychic derangement may appear when corticosteroids are used.

Use corticosteroids cautiously in patients with ocular herpes simplex because of possible corneal ulceration and perforation.

If any changes indicating metabolic alkalosis are noted, hydrocortisone should be reduced or stopped, and potassium chloride administered. Diuretics may provoke a further dangerous loss of potassium.

Potassium salts must be avoided or taken with great caution in the presence of renal impairment or cardiac decompensation. Although hypokalemia is an uncommon complication, it may occur quite suddenly. The prophylactic administration of 2 to 4 g daily of potassium chloride is advisable when maintenance dosage exceeds 80 mg a day. Note that the tissues may be low in potassium even when blood potassium concentrations appear adequate.

Hydrocortisone causes gluconeogenesis; therefore, hyperglycemia and glycosuria may occur, glucose tolerance may be altered, and diabetes mellitus may be aggravated. These effects usually are reversible on discontinuation of therapy, or sometimes with a decrease in dosage.

Protein metabolism may be affected in many patients, especially when high dosage is used. Continued use of large doses may produce a negative nitrogen balance. This can usually be prevented by placing the patient on a high protein diet.

Controlled clinical trials show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect in alleviating exacerbations of multiple sclerosis (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Although salt and water retention may occur, it is frequently followed by spontaneous diuresis on continued administration of hydrocortisone. Usually, there is only a slight gain in weight and minimal dependent oedema.

Fluid and electrolyte alterations: sodium retention; potassium loss; fluid retention; congestive heart failure in susceptible patients; hypokalemic alkalosis; hypertension.

Musculoskeletal: muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fracture; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones.

Gastrointestinal: pancreatitis; abdominal distention; ulcerative oesophagitis; nausea; peptic ulceration.

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Dermatologic: impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythemia; increased sweating.

Neurological: convulsions; increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment; vertigo; headache; psychic derangements.

Endocrine: menstrual irregularities; development of Cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exopthalmos.

Metabolic: negative nitrogen balance due to protein catabolism.

Immune System: opportunistic infections; hypersensitivity reactions including anaphylaxis.

The following additional adverse reactions are related to parenteral corticosteroid therapy: rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; post-injection flare (following intra-articular use); Charcot like arthropathy.

OVERDOSAGE

There is no clinical syndrome of acute overdosage with hydrocortisone sodium succinate. Hydrocortisone is dialyzable.

DOSAGE AND ADMINISTRATION

This preparation may be administered by intravenous injection by intravenous infusion or by intramuscular injection; the preferred method for initial emergency use being intravenous injection. Intramuscular administration leads to a slower rate of absorption.

Therapy is initiated by the administration of hydrocortisone intravenous over a period of 30 seconds (e.g., 100 mg) to 10 minutes (e.g., 500 mg or more). In general, high-dose corticosteroid therapy should be continued only until the patient's condition has stabilized, usually not beyond 48 to 72 hours.

The initial dose of hydrocortisone is 100 to 500 mg or more depending on the severity of the condition. This dose may be repeated at intervals of 2, 4, or 6 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 weight.

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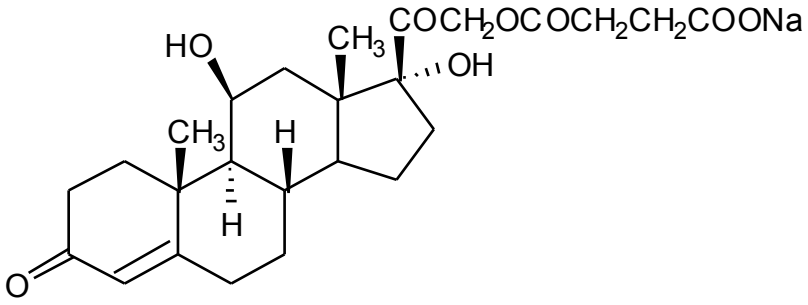
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: hydrocortisone sodium succinate
Systematic Chemical Name: pregn-4-ene-3,20-dione, 21-(3-carboxy-1-oxopropoxy))-11ß, 17α-dihydroxy-, monosodium salt.



Molecular Formula: $C_{25}H_{33}NaO_8$
Molecular Weight: 484.52
Description: A white or nearly white, odourless, hygroscopic, amorphous, very water soluble solid.

Composition

Each vial contains hydrocortisone sodium succinate and the buffer monobasic sodium phosphate/dibasic sodium phosphate, without preservative. Prepared by freeze-drying, having been filled into the vial in the form of a true solution.

COMPOSITION

	100 mg	250 mg	500 mg	1 g
Hydrocortisone (as hydrocortisone sodium succinate)	100 mg	250 mg	500 mg	1000 mg
Monobasic Sodium Phosphate Anhydrous	0.9 mg	2.0 mg	4.0 mg	8.0 mg
Dibasic Sodium Phosphate Dried	9.1 mg	23 mg	45 mg	87 mg

Stability and Storage

Store unreconstituted product at controlled temperature (15° to 30°C).

Reconstituted Solutions

IV/IM Injection: Reconstitute with Sterile Water for Injection, or if required, Bacteriostatic Water for Injection (benzyl alcohol as preservative) as follows:

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RECONSTITUTION

Hydrocortisone strength/vial	VOLUME OF DILUENT TO ADD (mL/vial)	APPROXIMATE AVAILABLE VOLUME (mL)	NOMINAL CONCENTRATION (mg/mL)
100 mg	1.8	2	50
250 mg	1.8	2	125
500 mg	3.8	4	125
1 g	7.3	8	125

Electrolyte content per millilitre of reconstituted solution: 100 mg vial-<1 mMol sodium; 250 mg vial-<1 mMol sodium; 500 mg vial-<1 mMol sodium;1 g vial-<1 mMol sodium.

When reconstituted with Sterile Water for Injection, (which is without bacteriostat), **use as a single use vial; discard unused portion.** Use immediately, since no preservatives are present, although studies support the chemical stability of 50 mg/mL and 125 mg/mL solutions in Sterile Water for Injection for 3 days. When resonstituted with Bacteriostatic Water for Injection, discard solutions, stored at controlled room temperature (15 to 30 °C) protected from light, after 3 days.

Freezing: Studies have shown reconstituted hydrocortisone 50 mg/mL and 125 mg/mL to be physically and chemically stable after one month of freezing. Once thawed, the above guidelines should be followed for hydrocortisone.

Further dilution is not necessary for intravenous or intramuscular injection.

Preparation of solution: Loosen powder. Hold vial horizontally and rotate while directing the stream of diluent against the wall of the vial. Shake vial after all the diluent is added. Use solution only if it is clear.

Parenteral Products

IV Infusion: For intravenous infusion, the reconstituted solution may be diluted as follows:
100 mg solution may be added to 100 to 1000 mL of 5% Dextrose in Water (or isotonic saline solution or 5% dextrose in isotonic saline solution if the patient is not on sodium restriction).
250 mg solution may be added to 250 to 1000 mL of the same infusion solutions.
500 mg solution may be added to 500 to 1000 mL of the same infusion solutions.
1 g solution may be added to 1000 mL of the same infusion solutions.

In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg of hydrocortisone may be added to 50 mL of the above infusion solutions. The resulting solutions are stable for at least 4 hours and may be administered either directly or by intravenous piggy back.

The stability of hydrocortisone in Dextrose 5% in Water, or Sodium Chloride Injection, 0.9%, at a concentration of <1 mg/mL, at room temperature, is at least 4 hours. Discard unused diluted solutions after this time.

AVAILABILITY OF DOSAGE FORMS

Pr Hydrocortisone Sodium Succinate for Injection is supplied in clear glass vials containing hydrocortisone 100, 250, 500 mg or 1 g (present as hydrocortisone sodium succinate).

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