

CORTROPHIN®-Zinc
(sterile corticotropin zinc
hydroxide suspension, USP)

DESCRIPTION

Cortrophin®-Zinc (sterile corticotropin zinc hydroxide suspension USP) is a sterile aqueous suspension of purified corticotropin (ACTH) with zinc hydroxide for repository action. It is available in a concentration of 40 USP units of corticotropin per mL which will provide therapeutic ACTH activity for a period from one to three days depending upon individual patient requirements. Each mL also contains 2 mg of zinc (as the hydroxide), 0.67 mg of dibasic sodium phosphate and 1% benzyl alcohol (preservative). The pH is adjusted with HCl and NaOH and the suspension is made isotonic with NaCl. Administration is by intramuscular injection into the gluteal muscle to avoid any possible local reaction. This is a fine aqueous suspension which flows readily through a 24–26 gauge hypodermic needle. Porcine ACTH is reported to have the following structural formula:

Ser- 1	Tyr- 2	Ser- 3	Met- 4	Glu- 5	His- 6	Phe- 7	Arg- 8	Trp- 9	Gly- 10	Lys 11
-Pro 12	-Val 13	-Gyl 14	-Lys 15	-Lys 16	-Arg 17	-Arg 18	-Pro 19	-Val 20	-Lys 21	-
								NH ₂		
Val- 22	Tyr- 23	Pro- 24	Asp- 25	Gly- 26	Ala- 27	Glu- 28	Asp- 29	Glu- 30	Leu- 31	Ala- 32
-Glu 33	-Ala 34	-Phe 35	-Pro 36	-Leu 37	-Glu 38	-Phe 39				

CLINICAL PHARMACOLOGY

ACTH is the anterior pituitary hormone which stimulates the functioning human adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Prolonged administration of large doses of ACTH induces hyperplasia and hypertrophy of the adrenal cortex with continuous high output of cortisol, corticosterone, and weak androgens. ACTH acts to stimulate the *synthesis* of adrenocortical hormones. If it facilitates the release of preformed steroids from the adrenal cortex at all, this effect is overshadowed by the greater effect on synthesis. ACTH is readily absorbed from intramuscular injection.

INDICATIONS AND USAGE

Cortrophin®-Zinc is indicated for diagnostic testing of adrenocortical function. Cortrophin®-Zinc has limited therapeutic value in those conditions responsive to corticosteroid therapy; however, corticosteroid therapy is considered to be the treatment of choice. Cortrophin®-Zinc may be employed in the following disorders:

1. *Endocrine disorders:*
Nonsuppurative thyroiditis.
Hypercalcemia associated with cancer.

2. *Rheumatic disorders:*
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Psoriatic arthritis.
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
Ankylosing spondylitis.
Acute and subacute bursitis.
Acute nonspecific tenosynovitis.
Acute gouty arthritis.
Synovitis of osteoarthritis.
Epicondylitis.
3. *Collagen diseases:*
During an exacerbation or as maintenance therapy in selected cases of:
Systemic lupus erythematosus.
Systemic dermatomyositis (polymyositis).
Acute rheumatic carditis.
4. *Dermatologic diseases:*
Pemphigus.
Bullous dermatitis herpetiformis.
Severe erythema multiforme (Stevens-Johnson syndrome).
Exfoliative dermatitis.
Severe psoriasis.
Severe seborrheic dermatitis.
Mycosis fungoides.
5. *Allergic states:*
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment.
Seasonal or perennial allergic rhinitis.
Bronchial asthma.
Contact dermatitis.
Atopic dermatitis.
Serum sickness
6. *Ophthalmic diseases:*
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
Allergic conjunctivitis.
Keratitis.
Herpes zoster ophthalmicus.
Iritis and iridocyclitis.
Diffuse posterior uveitis and choroiditis.
Optic neuritis.

Sympathetic ophthalmia.
Chorioretinitis.
Anterior segment inflammation.
Allergic corneal marginal ulcers.

7. *Respiratory diseases:*

Symptomatic sarcoidosis.
Loeffler's syndrome not manageable by other means.
Berylliosis.
Fulminating or disseminated pulmonary tuberculosis when used concurrently with antituberculous chemotherapy.
Aspiration pneumonitis.

8. *Hematologic disorders:*

Acquired (autoimmune) hemolytic anemia.
Secondary thrombocytopenia in adults.
Erythroblastopenia (RBC anemia).
Congenital (erythroid) hypoplastic anemia.

9. *Neoplastic diseases:*

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

10. *Edematous States:*

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

11. *Gastrointestinal diseases:*

To tide the patient over a critical period of the disease in:
Ulcerative colitis.
Regional enteritis.

12. *Nervous system:*

Acute exacerbation of multiple sclerosis.

13. *Miscellaneous:*

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate anti-tuberculous chemotherapy.
Trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS

When any of the following conditions are present:

Cortrophin[®]-Zinc is contraindicated in patients with a history of hypersensitivity reaction to corticotropin or any of the inactive ingredients of Cortrophin[®]-Zinc. Reactions have included anaphylaxis and angioedema.

Sclerodema, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of peptic ulcer, congestive heart failure, hypertension, or sensitivity to proteins derived from porcine sources.

Treatment of conditions listed within the indications section when they are accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction.

Not for intravenous or subcutaneous administration.

WARNINGS

Chronic administration of corticotropin may lead to adverse side effects which are not reversible. Corticotropin may only suppress symptoms and signs of chronic disease without altering the natural course of the disease. Cortrophin[®]-Zinc should not be administered for treatment until adrenal responsiveness has been verified with the route of administration which will be utilized during treatment, i.e. intramuscularly. A rise in urinary and plasma corticosteroid values provides direct evidence of a stimulatory effect. Hypersensitivity reactions including anaphylaxis and angioedema have been reported. Prolonged administration of corticotropin increases the risk of hypersensitivity reactions. Although the action of corticotropin is similar to that of exogenous adrenocortical steroids the quantity of adrenocorticoid may be variable. In patients who receive prolonged corticotropin therapy the additional use of rapidly acting corticosteroids before, during, and after an unusual stressful situation is indicated.

Prolonged use of corticotropin may produce posterior subcapsular cataracts and glaucoma with possible damage to the optic nerves.

Corticotropin may mask some signs of infection, and new infections, including those of the eye, due to fungi or viruses that may appear during its use. There may be decreased resistance and inability to localize infection when corticotropin is used.

Corticotropin can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. Corticotropin increases calcium excretion.

While on corticotropin therapy, patients should not be vaccinated against smallpox. Other immunization procedures should be undertaken with caution in patients who are receiving corticotropin, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

PRECAUTIONS

General

Patients with latent tuberculosis or tuberculin reactivity who receive corticotropin should be closely observed as reactivation of the disease may occur. During prolonged corticotropin therapy, these patients should receive chemoprophylaxis.

Skin testing should be performed prior to treatment of all patients with suspected sensitivity to porcine protein. Immediately following intramuscular administration of corticotropin patients should be observed carefully for sensitivity reactions.

Relative adrenocortical insufficiency induced by prolonged corticotropin therapy may be minimized by gradual reduction in corticotropin dosage. This type of insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress during that period, hormone therapy should be reinstituted.

There is an enhanced effect of corticotropin in patients with hypothyroidism and in those with cirrhosis.

The lowest possible dosage of corticotropin should be used to control the condition under treatment and when reduction in dosage is possible the reduction should be gradual as should discontinuation of therapy.

Corticotropin should be administered for treatment only when the disease is intractable to more conventional therapy. Corticotropin should be adjunctive and not the sole therapy in the treatment of a disease.

Since maximal corticotropin stimulation of the adrenals may be limited during the first few days of treatment, other drugs should be administered when an immediate therapeutic effect is desirable.

When infection is present, appropriate anti-infective therapy should be administered during corticotropin treatment and following discontinuation of corticotropin therapy.

Treatment of acute gouty arthritis should be limited to a few days. Since rebound attacks may occur when corticotropin is discontinued, conventional concomitant therapy should be administered during corticotropin treatment and for several days after it is stopped.

Psychic derangements may appear when corticotropin is used, ranging from euphoria, insomnia, mood swings, personality changes, and depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticotropin. Corticotropin should be used with caution in patients with diabetes, abscess, pyogenic infections, diverticulitis, renal insufficiency, and myasthenia gravis.

Although controlled clinical trials have shown ACTH to be effective in speeding the resolution of acute exacerbations of multiple sclerosis they do not show that it affects the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of ACTH are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION section.)

Since complications of treatment with ACTH 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.

Drug Interactions

Aspirin should be used cautiously in conjunction with corticotropin in hypoprothrombinemia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis – fetal abnormalities have been observed in experimental animals.

Carcinogenesis, Impairment of Fertility – since studies have not been performed to evaluate carcinogenic potential or potential impairment of fertility, physicians should weigh the potential risk/benefit ratio before using ACTH.

Pregnancy – Pregnancy Category C. Animal reproduction studies have not been conducted with corticotropin. It is also not known whether corticotropin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticotropin should be given to a pregnant woman only if clearly needed.

Nursing Mothers – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Cortrophin[®]-Zinc a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Usage – Safety and effectiveness in children have not been established. Growth and development of infants and children on prolonged corticotropin therapy should be carefully observed.

ADVERSE REACTIONS

The following adverse reactions are placed in decreasing order of severity within their own subclassification.

Fluid and Electrolyte Disturbances

Potassium loss.

Hypokalemia alkalosis.

Calcium loss.

Sodium retention.

Fluid retention.

Musculoskeletal

Pathologic fracture of long bones.

Vertebral compression fractures.

Osteoporosis.

Aseptic necrosis of femoral and humeral heads.

Steroid myopathy.

Loss of muscle mass.

Muscle weakness.

Gastrointestinal

Pancreatitis.

Ulcerative esophagitis.

Peptic ulcer with possible perforation and hemorrhage.

Abdominal distension.

Dermatologic

Impaired wound healing.

Petechiae and ecchymoses.

Suppression of skin test reactions.

Thin fragile skin.

Hyperpigmentation.

Acne.

Facial erythema.

Increased perspiration.

Cardiovascular

Congestive heart failure.

Hypertension.

Necrotizing angitis.

Neurological

Increased intracranial pressure with papilledema (pseudo-tumor cerebri), usually after treatment.

Convulsions.

Vertigo.

Headache.

Endocrine

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness.

Increased requirements for insulin or oral hypoglycemic agents in diabetics.

Suppression of growth in children.

Development of Cushingoid state.

Manifestations of latent diabetes mellitus.

Decreased carbohydrate tolerance.

Hirsutism

Menstrual irregularities.

Ophthalmic

Glaucoma with possible damage to optic nerve.

Increased intraocular pressure.

Posterior subcapsular cataracts.

Exophthalmos.

Metabolic

Negative nitrogen balance due to protein catabolism.

Allergic reactions

Especially in those who have exhibited allergic responses to proteins; these responses may manifest themselves as skin reactions, dizziness, nausea, vomiting, anaphylaxis, including anaphylactic shock, respiratory compromise, angioedema, urticaria.

Miscellaneous

Prolonged ACTH use may result in antibodies to it and loss of stimulatory effect.

Abscess.

DOSAGE AND ADMINISTRATION

Standard tests for verification of adrenal responsiveness to corticotropin may utilize as much as 80 units as a single injection or one or more injections of a lesser dosage. Verification tests should be performed prior to treatment with corticotropin. The test should utilize the route of administration proposed for treatment. Following verification dosage should be individualized according to the disease under treatment and the general medical condition of each patient. Frequency and dose of the drug should be determined by considering severity of the disease, plasma and urine corticosteroid levels and the initial response of the patient. Only gradual change in dosage schedules should be attempted, after full drug effects have become apparent.

In the treatment of acute exacerbations of multiple sclerosis daily intramuscular doses of 80-120 units for two to three weeks may be administered.

The chronic administration of more than 40 units daily may be associated with uncontrollable adverse effects.

When reduction in dosage is indicated this should be accomplished gradually by increasing the duration between injections or decreasing the quantity of corticotropin injected or by a combination of the above. During reduction of dosage, careful consideration should be given to the disease being treated, the general medical condition of the patient and the duration over which corticotropin was administered.

Cortrophin®-Zinc should be injected deeply into the gluteal muscle and not given subcutaneously.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit.

HOW SUPPLIED

Available in 5-mL vials containing 40 USP units of corticotropin (ACTH) per mL NDC# [PENDING].

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION – Federal law prohibits dispensing without prescription.

Distributed by:
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