PRESCRIBING INFORMATION

CORTIFOAM

Hydrocortisone Acetate USP 10%

Rectal Anti-Inflammatory Corticosteroid Foam

Paladin Labs Inc.
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Control No: 131117

PRESCRIBING INFORMATION

NAME OF DRUG

CORTIFOAM

(Hydrocortisone Acetate USP 10%)

THERAPEUTIC CLASSIFICATION

Rectal Anti-Inflammatory Corticosteroid Foam

ACTION AND CLINICAL PHARMACOLOGY

The action of Cortifoam (hydrocortisone acetate USP 10%) appears to be due to a local anti-inflammatory effect of hydrocortisone acetate on the mucosa rather than as a result of a systemic effect due to absorption of hydrocortisone.

INDICATIONS

Cortifoam (hydrocortisone acetate USP 10%) is indicated as adjunctive therapy in the treatment of ulcerative colitis of the sigmoid colon, proctosigmoiditis, granular proctitis and ulcerative proctitis.

CONTRAINDICATIONS

Contraindications to the use of intrarectal steroids include obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, extensive fistulas and sinus tracts. Tuberculosis (active, latent or questionably healed), ocular herpes simplex, varicella, vaccinia, and acute psychosis are usually considered contraindications to the use of corticosteroids.

Other contraindications include active peptic ulcer, acute glomerulonephritis, myasthenia gravis, osteoporosis, diverticulitis, thrombophlebitis, psychic disturbances, pregnancy, diabetes, hyperthyroidism, acute coronary disease, hypertension, limited cardiac reserve, and local or systemic infections, including fungal or exanthematous diseases. Where these conditions exist, the expected benefits from steroid therapy must be weighed against the risks involved in its use.

Cortifoam (hydrocortisone acetate USP 10%) is also contraindicated in systemic fungal infection and in the presence of hypersensitivity to any of its components.

WARNINGS

CAUTION: Contents are flammable and the aerosol container may explode if heated.

Do not insert any part of the aerosol container into the anus.

Do not use in presence of an open flame or spark. Contents of the container are under pressure. Do not refrigerate. Do not place in hot water or near radiators, stoves or other sources of heat. Do not incinerate or puncture the aerosol container or store at temperatures over 50 C.

Because Cortifoam (hydrocortisone acetate USP 10%) is not expelled, systemic hydrocortisone absorption may be greater from Cortifoam than from corticosteroid enema formulations. If there is no evidence of clinical or proctologic improvement within two or three weeks after starting Cortifoam therapy, or if the patient's condition worsens, discontinue the drug.

Signs and symptoms of intestinal perforation and peritonitis may be difficult to detect during corticosteroid treatment.

PRECAUTIONS

General:

A complete rectal examination to rule out serious pathology and extension of the disease process should be completed before instituting therapy.

Do not use on infected lesions unless accompanied with anti-infective agents.

Steroid therapy should be administered with caution in patients with severe ulcerative disease because these patients are predisposed to perforation of the bowel wall. Where surgery is imminent, it is hazardous to wait more than a few days for a satisfactory response to medical treatment. General precautions common to all corticosteroid therapy should be observed during treatment with Cortifoam (hydrocortisone acetate USP 10%). These include gradual withdrawal of therapy to allow for possible adrenal insufficiency and awareness of possible growth suppression in children. Patients should be kept under close observation, for as with all drugs, rare individuals may react unfavorably under certain conditions. If severe reactions or idiosyncrasies occur, steroids should be discontinued immediately and appropriate measures instituted. Do not employ in immediate or early postoperative period following ileorectostomy.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Use in Pregnancy:

Steroids should not be used during pregnancy since safety during pregnancy has not been fully established.

If corticosteroids must be administered during pregnancy, particularly during the third trimester, the newborn infant must be observed closely for signs of hypoadrenalism, and the appropriate therapy administered if needed.

Nursing Mothers:

Mothers using Cortifoam should be advised not to nurse.

ADVERSE REACTIONS

Corticosteroid therapy may produce side effects which include moon face, fluid retention, excessive appetite and weight gain, abnormal fat deposits, mental symptoms, hypertrichosis, acne, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, menstrual disorders, neuropathy, peptic ulcer, decreased glucose tolerance, hypokalemia, adrenal insufficiency, necrotizing angiitis, hypertension, pancreatitis and increased intraocular pressure. In children, suppression of growth may occur. Increased intracranial pressure may occur and possibly account for headache, insomnia and fatigue. Subcapsular cataracts may result from prolonged usage. Long-term use of all corticosteroids results in catabolic effects characterized by negative protein and calcium balance. Osteoporosis, spontaneous fractures and aseptic necrosis of the hip and humerus may occur as part of this catabolic phenomenon. Where hypokalemia and other symptoms associated with fluid and electrolyte imbalance call for potassium supplementation and salt poor or salt-free diets, these may be instituted and are compatible with diet requirements for ulcerative proctitis.

Local effects of itching and burning have been reported following rectal use.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Acute toxicity, even with massive doses is not a clinical problem. Chronic toxicity involves manifestations of the physiologic effects described above and include Cushingoid appearance, muscle weakness, osteoporosis, posterior subcapsular cataracts, peptic ulcers, hypertension, psychosis, and growth suppression in children. Glaucoma, pancreatitis, reactivation of tuberculosis and poor wound healing may occur. Sodium and fluid retention with potassium loss occur to varying degrees, depending upon the mineralocorticoid effects of the particular corticosteroid.

Treatment:

Acute overdosage probably requires no treatment. Acute overdosage requires no tapering as in withdrawal of patients on long-term administration. If there is any question that other drugs have

been ingested simultaneously, then standard measures for those drugs should be followed as per instructions for their management.

1) Avoid chronic dosage for durations greater than 3 weeks when possible.

2) When chronic dosage for periods greater than 3 weeks is essential, attempts should be made to manage the underlying disease if possible with alternate day dosage using single daily doses on alternate mornings of shorter acting preparations such as prednisone, prednisolone or methylprednisolone.

3) Even with alternate day dosage of appropriate agents, continued attempts should be made to minimize dosage compatible with maintained control of the underlying disease.

4) The diet should have adequate protein content but caloric restrictions should be considered because of the apparent appetite stimulating properties of the corticosteroids.

5) The ultimate treatment of toxicity should be avoidance of inappropriate usage or if toxicity is already present, withdrawal of the corticosteroids and conventional management of those effects which are treatable such as peptic ulcers, cataracts and hypertension.

DOSAGE AND ADMINISTRATION

The usual dose is one applicator full once or twice daily for two or three weeks, and every second day thereafter, administered rectally. The patient direction insert describes how to use the aerosol container and applicator. Satisfactory response usually occurs within five to seven days marked by a decrease in symptoms. Symptomatic improvement should not be used as the sole criterion for evaluating efficacy. Sigmoidoscopy is also recommended to judge dosage adjustment, duration of therapy and rate of improvement.

The hydrocortisone acetate is present at 10% in a foam vehicle, which is aerosolized in an aerosol container. A special applicator is provided which is designed to deliver approximately 6.5 mL (900 mg) of foam, 80 mg of hydrocortisone (90 mg hydrocortisone acetate).

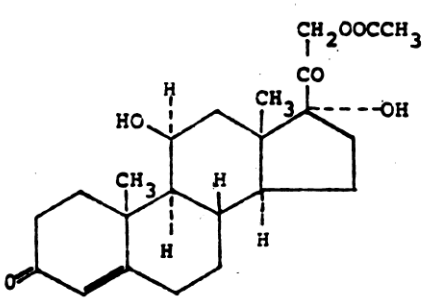
PHARMACEUTICAL INFORMATION

Drug Substance:

Common Name: Hydrocortisone Acetate

Chemical Name: Pregn-4-ene-3, 20-dione, 21-(acetyloxy)-11, 17-dihydroxy-, (11)-.

Molecular Weight: 404.50
Structural Formula:



Physical Form: white to practically white, odourless crystalline powder

Solubility: insoluble in water, slightly soluble in alcohol and chloroform

Melting point: 220 C.

Composition:

Contains hydrocortisone acetate USP 10% as the sole active ingredient in a foam containing propylene glycol, ethoxylated stearyl alcohol, polyoxyethylene-10 stearyl ether, cetyl alcohol, methylparaben, propylparaben, triethanolamine, water and inert propellants, isobutane and propane.

AVAILABILITY OF DOSAGE FORMS

Cortifoam (hydrocortisone acetate USP 10%) is supplied in an aerosol container with a special rectal applicator. Each applicatorful delivers approximately 900 mg of foam containing approximately 80 mg of hydrocortisone as 90 mg of hydrocortisone acetate. The 15 g aerosol container will deliver approximately 14 applications.

Contents of the container are under pressure and are flammable. Do not use in the presence of an open flame or spark.

Do not puncture or incinerate the aerosol container. Store at room temperature, not over 50° C.

PHARMACOLOGY[1]

Clinical Pharmacology:

A bioavailability study was designed and conducted by William H. Barr, Pharm. D., PhD at the Department of Pharmacy and Pharmaceutics and the Department of Gastroenterology at Medical College of Virginia/Virginia Commonwealth University to assess the extent of absorption of biologically active hydrocortisone into the systemic circulation from the rectal route (from Cortifoam rectal foam) versus oral administration. The study was required to detect with a 95% confidence limit a 25% difference in the amount absorbed. To decrease the intra and intersubject variability in both absorption and first pass metabolism, a deuterated and a non-deuterated hydrocortisone were administered simultaneously.

In the study, seven normal male student subjects received orally 50 mg of deuterated hydrocortisone alcohol initially dissolved in 10 mL 95% alcohol and diluted in 100 mL distilled water. The subjects immediately afterward received a self-administered dose of 50 mg non-deuterated hydrocortisone as the acetate in about 5 mL of the rectal foam. To suppress endogenous hydrocortisone each subject received a 0.75 mg tablet of dexamethasone the night before and again on the morning of the study. The subjects received the hydrocortisone after a 12-hour fast and ate a light fat-free breakfast and a light lunch.

The subjects were ambulatory throughout the study. Blood samples were taken just prior to dosing to determine base levels of endogenous hydrocortisone and at 0, 10, 20, 40, 70, 100, 140, 180, 240, 360, 600 and 720 minutes. The blood was separated and the plasma frozen until assayed. The ratio of deuterated hydrocortisone to normal hydrocortisone was determined by mass spectrometer in conjunction with a gas chromatograph.

The apparent bioavailabilities of rectal versus oral ranged from 2.6 - 30.9%. However, the endogenous hydrocortisone as evident from zero time, as the result of incomplete endogenous hydrocortisone suppression with dexamethasone, was applied to the bioavailability data and the actual bioavailabilities dropped to 1 - 10% with an average bioavailability 3% rectal compared with oral administration.

The study concluded that the rectal absorption of hydrocortisone is very limited (of the order of 10% or less), and the beneficial results of Cortifoam appear to be due to local effects on the mucosa rather than a result of systemic effects due to absorbed hydrocortisone.

Pharmacology:

[1] This section is taken without change from the original product monograph dated February 9, 1983.

The effects of corticosteroids are numerous and widespread. They influence carbohydrate, protein, fat and purine metabolism; electrolyte and water balance; and the functions of the cardiovascular system, the kidney, skeletal muscle, the nervous system and other organs and tissues. Furthermore, the corticosteroids endow the organism with the capacity to resist many types of noxious stimuli and environmental change.

In Cortifoam, the most significant pharmacological property of hydrocortisone is its anti-inflammatory property. Hydrocortisone and the synthetic analogs of hydrocortisone have the capacity to prevent or suppress the development of the local heat, redness, swelling and tenderness by which inflammation is recognized. At the microscopic level, they inhibit not only the early phenomena of the inflammatory process (edema, fibrin deposition, capillary dilatation, migration of leukocytes into the inflamed area, and phagocytic activity) but also the later manifestations (capillary proliferation, fibroblast proliferation, deposition of collagen, and, still later, cicatrization).

Although understanding of these effects is unsatisfactory, many observations have been made that have therapeutic relevance and that must be taken into account in explanatory formulations. Perhaps the most important of these for the physician is that corticosteroids inhibit the inflammatory response whether the inciting agent is radiant, mechanical, chemical, infectious, or immunological. In clinical terms, the administration of corticosteroids for their anti-inflammatory effects is palliative therapy; the underlying cause of the disease remains; the inflammatory manifestations are merely suppressed. It is this suppression of inflammation and its consequences that has made the corticosteroids such valuable therapeutic agents - indeed, at times lifesaving. It is also this property that gives them a nearly unique potential for therapeutic disaster. The signs and symptoms of inflammation are expressions of the disease process that are often used by the physician in diagnosis and in evaluating the effectiveness of treatment. These may be missing in patients treated with glucocorticoids.

Hydrocortisone and presumably other anti-inflammatory steroids are to be found in inflamed tissues, although they are not selectively concentrated there. Anti-inflammatory effects depend upon the direct local action of the steroids, since those that do not require metabolic modification for activity are very effective on topical application to skin or eye.

Several discrete effects of the steroids relevant to their anti-inflammatory properties are beginning to be understood. For example, a considerable amount is known about the inhibitory effects of the glucocorticoids on fibroblasts, phenomena that are of undoubted importance in the suppression of later phases of inflammation. The mechanism by which glucocorticoids inhibit accumulation of macrophages is to block the effect of the migration inhibitory factor (MIF), a lymphokine produced by an antigen activated lymphocyte, on macrophages; that is, the movement of these cells is no longer impeded and the macrophages no longer accumulate. It has also been found that hydrocortisone, when added to a mixture of cultured lymphocytes and monocytes, causes the appearance of a factor in the culture medium that stimulates the migration of polymorphonuclear leukocytes. This may account for suppression of infiltration by polymorphonuclear cells. The effects of glucocorticoids on neutrophils have been reviewed by Mishler. Low concentrations of glucocorticoids inhibit the formation by macrophages of an

activator of plasminogen, an effect that may contribute to their anti-inflammatory properties. There is also substantial evidence that the glucocorticoids inhibit release of arachidonic acid from phospholipids and thereby decrease formation of prostaglandins and related compounds, such as prostaglandin endoperoxides and thromboxane, which may play an important role in inflammation.

TOXICOLOGY[2]

Acute toxicity, even with massive doses, is not a clinical problem.

However, two categories of toxic effects are observed in the therapeutic use of adrenocorticosteroids: those resulting from withdrawal and those resulting from continued use of large doses. Acute adrenal insufficiency results from too rapid withdrawal of corticosteroids after prolonged therapy.

In addition to pituitary-adrenal suppression, the principle complications resulting from prolonged therapy with corticosteroids are fluid and electrolyte disturbances; hyperglycemia and glycosuria; increased susceptibility to infections including tuberculosis; peptic ulcers, which may bleed or perforate; osteoporosis; a characteristic myopathy; behavioral disturbances; posterior subcapsular cataracts; arrest of growth and Cushing's habitus, consisting in "moon face", "buffalo hump", enlargement of supraclavicular fat pads, "central obesity", striae, ecchymoses, acne and hirsutism.

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[2] This section is taken without change from the original product monograph dated February 9, 1983.

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12. Barr WH, Kline B, Beightol L and Zfass A. Bioavailability of hydrocortisone acetate rectal foam (CORTIFOAM®). Research Report, Medical College of Virginia, Virginia Commonwealth University, October 25, 1981.

[3] This section was revised when the prescribing info was updated in 1999. References 13, 14 & 15 were added.

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