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Celestone* Chronodose* Injection

Brand of betamethasone sodium phosphate and betamethasone acetate

FOR INTRAMUSCULAR, INTRA-ARTICULAR, PERIARTICULAR, INTRABURSAL, INTRADERMAL, AND INTRALESIONAL USE

Schering-Plough

DESCRIPTION

CELESTONE CHRONODOSE Injection is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. Each ml of CELESTONE CHRONODOSE Injection contains 3 mg betamethasone as betamethasone sodium phosphate and 3 mg betamethasone acetate. Inactive ingredients: Sodium phosphate monobasic, sodium phosphate dibasic, disodium edetate, benzalkonium chloride and water for Injection.

ACTIONS

CELESTONE CHRONODOSE Injection is a combination of soluble and slightly soluble betamethasone esters that provides potent anti-inflammatory, antirheumatic and antiallergic effects in the treatment of corticosteroid-responsive disorders. Prompt therapeutic activity is achieved by betamethasone sodium phosphate, which is absorbed quickly after injection. Sustained activity is provided by betamethasone acetate, which is only slightly soluble and becomes a repository for slow absorption, thereby controlling symptoms over a prolonged period.

Glucocorticosteroids, such as betamethasone, cause profound and varied metabolic effects and modify the body's immune response to diverse stimuli.

Betamethasone has high glucocorticosteroid activity and slight mineralocorticosteroid activity.

INDICATIONS AND USAGE

CELESTONE CHRONODOSE Injection is recommended in the therapy of severe and moderate diseases, in acute and chronic self-limited diseases responsive to systemic corticosteroid therapy and is especially useful in patients for whom treatment with oral corticosteroid medication is not feasible. Corticosteroid hormone therapy is an adjunct to, and not a replacement for, conventional therapy.

Recommended routes of administration are (1) intramuscular injection in allergic, dermatologic, rheumatic and other conditions responsive to systemic corticosteroids, including bursitis; (2) injection directly into the affected soft tissues in bursitis and associated inflammatory disorders of tendons such as tenosynovitis, and in inflammatory disorders of muscle such as fibrositis and myositis; (3) intra-articular and periarticular injection in rheumatoid arthritis and osteoarthritis; (4) intra-lesional injections in various dermatologic conditions; and (5) local injection in certain inflammatory disorders of the foot.

Representative conditions:

Rheumatic Disorders: Post-traumatic osteoarthritis, osteoarthritic synovitis, rheumatoid arthritis, acute and subacute bursitis, epicondylitis, acute nonspecific tenosynovitis, myositis, fibrositis, tendonitis, acute gouty arthritis, psoriatic arthritis, low back syndrome, lumbago, sciatica, coccygodynia, torticollis, ganglion cyst.

Collagen Diseases: Systemic lupus erythematosus, scleroderma, dermatomyositis.

Allergic States: Status asthmaticus, chronic bronchial asthma, seasonal or perennial allergic rhinitis, severe allergic bronchitis, contact dermatitis, atopic dermatitis, hypersensitivity reactions to drugs and insect bites.

Dermatologic Conditions: Localized, hypertrophic infiltrated lesions of lichen planus, psoriatic plaques, granuloma annulare and neurodermatitis (lichen simplex chronicus), keloids, discoid lupus erythematosus, necrobiosis lipoidica diabeticorum, alopecia areata.

Disorders of the Foot: Bursitis under heloma durum, under heloma molle, and under calcaneal spur; bursitis over hallus rigidus, and over digiti quinti varus; synovial cyst; tenosynovitis; periostitis of cuboid; acute gouty arthritis; metatarsalgia.

Antepartum use in the prevention of respiratory distress syndrome in premature infants: When deemed necessary to induce labor prior to the 32nd week of gestation or when premature birth before the 32nd week of gestation becomes inevitable because of obstetric complication, it is recommended that 2 ml (12 mg) of CELESTONE CHRONODOSE Injection be injected intramuscularly at least 24 hours before the expected time of delivery. A second dose (2 ml) should be given 24 hours later unless delivery has occurred.

CELESTONE CHRONODOSE Injection should also be considered for prophylactic treatment if the fetus is known to have a low lecithin/sphingomyelin ratio (or decreased foam stability test on amniotic fluid). The same dosage regimen as described for antepartum use in the prevention of respiratory distress syndrome in premature infants is recommended.

Corticosteroids are not indicated in the management of hyaline membrane disease after birth.

Neoplastic Diseases: For palliative management of leukemias and lymphomas in adults; acute leukemia of childhood.

DOSAGE AND ADMINISTRATION

DOSING REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE SPECIFIC DISEASE, ITS SEVERITY AND THE RESPONSE OF THE PATIENT.

Systemic Administration: Treatment of conditions requiring systemic corticosteroid effects can be carefully controlled by intramuscular injections of CELESTONE CHRONODOSE Injection. Its rapid and prolonged action make it suitable for initiation of therapy in acute conditions in which control of inflammation must be achieved quickly and then maintained. The repository action of the drug assists in the prevention of recrudescence from irregular maintenance of corticosteroid effects.

Treatment is initiated with an intramuscular injection of 1 ml of CELESTONE CHRONODOSE Injection in most conditions and repeated weekly, or more often, if necessary. In less severe disease, lower doses generally will suffice. In severe illness, such as status asthmaticus or disseminated lupus erythematosus, 2 ml might be required initially.

The initial dose should be maintained or adjusted until a satisfactory response is observed. If a satisfactory clinical response does not occur after a reasonable period of time, treatment with CELESTONE CHRONODOSE Injection should be discontinued and other appropriate therapy initiated.

Local Administration: If coadministration is desired, CELESTONE CHRONODOSE Injection may be mixed (in the syringe, not the vial) with 1% or 2% lidocaine hydrochloride, procaine hydrochloride, or similar local anesthetics using formulations which do not contain parabens. Anesthetics containing methylparaben, propylparaben, phenol, etc. should be avoided. The required dose of CELESTONE CHRONODOSE Injection is first withdrawn from the vial into the syringe. The local anesthetic is then drawn in, and the syringe is shaken briefly.

In bursitis (subdeltoid, subacromial and prepatellar), one intrabursal injection of 1 ml relieves pain and restores the full range of movement in a few hours. Several intrabursal injections at intervals of 1 to 2 weeks are usually required in recurrent acute bursitis and in acute exacerbations of chronic bursitis.

In tendonitis, myositis, fibrositis, tenosynovitis, peritendonitis, and periarticular inflammatory conditions, three or four local injections of 1 ml each at intervals of one to two weeks are recommended in most cases. Injection should be made into the affected tendon sheaths rather than into the tendons themselves. In periarticular inflammatory conditions, the painful area should be infiltrated. In ganglions of joint capsules, 0.5 ml is injected directly into the ganglion cysts.

In rheumatoid arthritis and osteoarthritis, relief of pain, soreness and stiffness may be experienced in 2 to 4 hours after intra-articular injection. Dosage ranges from 0.25 to 2 ml, according to the size of the joint to be injected: very large joints (hip), 1 to 2 ml; large joints (knee, ankle and shoulder), 1 ml; medium joints (elbow and wrist), 0.5 to 1 ml; and small joints (hand and chest), 0.25 to 0.5 ml. Relief usually lasts from 1 to 4 or more weeks. Using sterile technique, a 29 to 24 gauge needle on an empty syringe for aspiration is inserted into the synovial cavity and a few drops of synovial fluid are withdrawn to confirm that the needle is in the joint. The aspirating syringe is replaced by the syringe containing CELESTONE CHRONODOSE Injection and the injection is then made into the joint.

In intralesional treatment, 0.2 ml/cm2 of CELESTONE CHRONODOSE Injection is injected intradermally (not subcutaneously) using a tuberculin syringe with a 25 gauge, 1/2 inch (1.27 cm) needle. Care should be taken to deposit a uniform depot of medication intradermally. Total amount injected at all sites weekly should not exceed 1 ml.

CELESTONE CHRONODOSE Injection is also effective in the treatment of corticosteroid-responsive disorders of the foot. Bursitis under heloma durum (hard corn) has been controlled with two successive injections of 0.25 ml each. In conditions such as hallux rigidus (flexion deformity of the great toe), digiti quinti varus (inward deviation of the fifth toe) and acute gouty arthritis, onset of relief may be rapid. A tuberculin syringe with a 25-gauge, 3/4 inch (1.90 cm) needle is suitable for most injections into the foot. For most podiatric conditions doses of 0.25 to 0.5 ml at intervals of three to seven days are recommended. In acute gouty arthritis doses up to 1 ml may be necessary.

After a favorable response is obtained, the proper maintenance dosage should be determined by decreasing the initial dose in small decrements at appropriate time intervals until the lowest dose which will maintain an adequate clinical response is determined.

Exposure of the patient to stressful situations unrelated to the existing disease may necessitate an increased dose of CELESTONE CHRONODOSE Injection. If the drug is to be discontinued after long-term therapy, the dose should be decreased gradually.

DRUG AND LABORATORY TEST INTERACTIONS

Drug Interactions: Concurrent use of phenobarbital, phenytoin, rifampin or ephedrine may enhance the metabolism of corticosteroids, reducing their therapeutic effects.

Patients receiving both a corticosteroid and an estrogen should be observed for excessive corticosteroid effects.

Concurrent use of corticosteroids with potassium-depleting diuretics may enhance hypokalemia. Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. Corticosteroids may enhance the potassium depletion caused by amphotericin B. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.

Concurrent use of corticosteroids with coumarin-type anticoagulants may increase or decrease the anticoagulant effects, possibly requiring adjustment in dosage.

Combined effects of non-steroidal anti-inflammatory drugs or alcohol with glucocorticosteroids may result in an increased occurrence or increased severity of gastrointestinal ulceration.

Corticosteroids may decrease blood salicylate concentrations. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Dosage adjustments of an antidiabetic drug may be necessary when corticosteroids are given to diabetics.

Concomitant glucocorticosteroid therapy may inhibit the response to somatotropin.

Laboratory Test Interactions: Corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

ADVERSE REACTIONS

Adverse reactions to CELESTONE CHRONODOSE Injection, which have been the same as those reported for other corticosteroids, relate both to dose and to duration of therapy. Usually these reactions can be reversed or minimized by a reduction in dosage; this is generally preferable to withdrawal of drug treatment.

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

Musculoskeletal: muscle weakness, corticosteroid myopathy, loss of muscle mass; aggravation of myasthenic symptoms in myasthenia gravis; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones; tendon rupture; joint instability (from repeated intra-articular injections).

Gastrointestinal: hiccups, peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis.

Dermatologic: impaired wound healing; skin atrophy; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; suppressed reactions to skin tests; reactions such as allergic dermatitis, urticaria, angioneurotic edema.

Neurologic: convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache.

Endocrine: menstrual irregularities; development of cushingoid state; suppression of fetal intrauterine or childhood growth; 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 of insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure, glaucoma; exophthalmos.

Metabolic: negative nitrogen balance due to protein catabolism.

Psychiatric: euphoria, mood swings; severe depression to frank psychotic manifestations; personality changes; insomnia.

Other: anaphylactoid or hypersensitivity and hypotensive or shock-like reactions.

Additional adverse reactions related to parenteral corticosteroid therapy include rare instances of blindness associated with intralesional therapy around the face and head, hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, postinjection flare (following intra-articular use) and charcot-like arthropathy.

CONTRAINDICATIONS

CELESTONE CHRONODOSE Injection is contraindicated in patients with systemic fungal infections, in patients hypersensitive to betamethasone sodium phosphate, betamethasone acetate, other corticosteroids, or to any component of this product.

PRECAUTIONS

CELESTONE CHRONODOSE Injection is not for intravenous or subcutaneous use.

Strict aseptic technique is mandatory in the use of CELESTONE CHRONODOSE Injection.

CELESTONE CHRONODOSE Injection contains two betamethasone esters, one of which, betamethasone sodium phosphate, disappears rapidly from the injection site. The potential for systemic effect produced by this soluble portion of CELESTONE CHRONODOSE Injection should therefore be taken into account by the physician when using this preparation.

Since use of corticosteroids prophylactically beyond the 32nd week of gestation is still controversial, the risk/benefit ratio should be considered for mother and fetus when using corticosteroids beyond this gestational period.

Corticosteroids are not indicated in the management of hyaline membrane disease after birth and should not be administered to pregnant women with pre-eclampsia, eclampsia, or evidence of placental damage.

CELESTONE CHRONODOSE Injection should be administered intramuscularly with caution to patients with idiopathic thrombocytopenic purpura.

Intramuscular injections of corticosteroids should be given deep into large muscle masses to avoid local tissue atrophy.

Soft tissue, intralesional and intra-articular administration of a corticosteroid may produce systemic as well as local effects.

Examination of any joint fluid present is necessary to exclude a septic process. Local injection into a previously infected joint is to be avoided. A marked increase in pain and local swelling, further restriction of joint motion, fever and malaise are suggestive of septic arthritis. If the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Corticosteroids should not be injected into unstable joints, infected areas or intervertebral spaces. Repeated injections into joints of osteoarthritis may increase joint destruction. Avoid injecting corticosteroids directly into the substance of tendons because delayed appearance of tendon rupture has resulted.

Following intra-articular corticosteroid therapy, care should be taken by the patient to avoid overuse of the joint in which symptomatic benefit has been obtained.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

With long-term corticosteroid therapy, transfer from parenteral to oral administration should be considered after weighing the potential benefits and risks.

Dosage adjustments may be required with remission or exacerbation of the disease process, the patient's individual response to therapy and exposure of the patient to emotional or physical stress such as serious infection, surgery or injury. Monitoring may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.

Corticosteroids may mask some signs of infection, and new infections may appear during use. When corticosteroids are used, decreased resistance and inability to localize infection may occur.

Prolonged corticosteroid use may produce posterior subcapsular cataracts (especially in children), glaucoma with possible damage to the optic nerves, and may enhance secondary ocular infections due to fungi or viruses.

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be considered. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients receiving corticosteroids, especially high doses, because of possible hazards of neurological complications and lack of antibody response. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison disease.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice. This is of particular importance in children.

Corticosteroid therapy in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for management in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy, patients should receive chemoprophylaxis. If rifampin is used in a chemoprophylactic program, its enhancing effect on metabolic hepatic clearance of corticosteroids should be considered; adjustment in corticosteroid dosage may be required.

The lowest possible dose of corticosteroid should be used to control the condition under treatment; when dosage reduction is possible, it should be gradual.

Drug-induced secondary adrenocortical insufficiency may result from too rapid corticosteroid withdrawal and may be minimized by gradual dosage reduction. Such relative insufficiency may persist for months after discontinuation of therapy; therefore, if stress occurs during that period, corticotherapy should be reinstituted. If the patient is receiving corticosteroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticosteroid should be administered concurrently.

Corticosteroid effect is enhanced in patients with hypothyroidism or in those with cirrhosis.

Cautious use of corticosteroids is advised in patients with ocular herpes simplex because of possible corneal perforation.

Psychic derangements may appear with corticosteroid therapy. Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Corticosteroids should be used with caution in: nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Since complications of glucocorticosteroid treatment are dependent on dose, size and duration of treatment, a risk/benefit decision must be made with each patient.

Since corticosteroid administration can disturb growth rates and inhibit endogenous corticosteroid production in infants and children, the growth and development of these patients receiving prolonged therapy should be followed carefully.

Corticosteroids may alter the motility and number of spermatozoa in some patients.

USAGE DURING PREGNANCY AND LACTATION

Since controlled human reproduction studies have not been done with corticosteroids, the use of these drugs at any time during pregnancy or in women of childbearing age requires that the possible benefits of the drug be weighed against the potential hazards to the mother and fetus.

Published data show that the use of prophylactic corticosteroids beyond the 32nd week of gestation is still controversial. Therefore, the physician should weigh the benefits against the potential hazards to the mother and the fetus when using corticosteroids beyond the 32nd week of gestation.

Corticosteroids are not indicated in the management of hyaline membrane disease after birth.

In the prophylactic treatment of hyaline membrane disease in premature infants, corticosteroids should not be administered to pregnant women with pre-eclampsia, eclampsia, or evidence of placental damage.

Infants born of mothers who received substantial doses of corticosteroid during pregnancy should be observed carefully for signs of hypoadrenalism. When mothers were given betamethasone injections prenatally, the infants had transient suppression of fetal growth hormone and presumably of those pituitary hormones, which regulate corticosteroid production by both the definitive and fetal zones of the fetal adrenal glands. However, the suppression of fetal hydrocortisone did not interfere with the pituitary-adrenocortical responses to stress after birth.

Corticosteroids cross the placental barrier and appear in breast milk of nursing mothers.

Because transplacental passage of corticosteroids occurs, newborn and young infants born of mothers who were dosed with corticosteroids throughout most or some portion of their pregnancy should be examined carefully for the possible very rare occurrence of congenital cataracts.

Women who have been on corticosteroids during pregnancy should be monitored during and after labor and delivery for any indication of adrenal insufficiency because of the stresses associated with childbirth.

Because of the potential for unwanted adverse effects from CELESTONE CHRONODOSE Injection in nursing infants, 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.

OVERDOSAGE INFORMATION:

Symptoms: Acute overdosage with glucocorticosteroids, including betamethasone, is not expected to lead to a life-threatening situation. Except at the most extreme dosages, a few days of excessive glucocorticosteroid dosing is unlikely to produce harmful results in the absence of specific contraindications, such as in patients with diabetes mellitus, glaucoma, or active peptic ulcer, or in patients on medications such as digitalis, coumarin-type anticoagulants or potassium-depleting diuretics.

Treatment: Complications resulting from the metabolic effects of the corticosteroid or from deleterious effects of the basic or concomitant illnesses or resulting from drug interactions should be handled as appropriate.

Maintain adequate fluid intake and monitor electrolytes in serum and urine, with particular attention to sodium and potassium balance. Treat electrolyte imbalance if necessary.

HOW SUPPLIED

1 ml amp. box of 1

STORAGE

Shake well before using. Store between 2° and 25° C. Protect from light and freezing.

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