CELESTONE Injection
Schering-Plough

DESCRIPTION
CELESTONE Injection is a sterile solution of betamethasone sodium phosphate, the sodium salt of the 21-phosphate ester of betamethasone. Each ml CELESTONE Injection contains 5.3 mg betamethasone sodium phosphate equivalent to 4 mg betamethasone.

ACTIONS
CELESTONE Injection provide potent anti-inflammatory, antirheumatic and antiallergic effects in the treatment of corticosteroid-responsive disorders. 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 Injection is indicated in the management of various endocrine, rheumatic, collagen, dermatologic, allergic, ophthalmic, gastrointestinal, respiratory, hematologic and other diseases known to be responsive to corticosteroid therapy. Corticosteroid hormone therapy is an adjunct to, and not a replacement for, conventional therapy. This preparation is indicated when a rapid, intense corticosteroid effect is necessary or desirable.

Endocrine Disorders
Primary or secondary adrenocortical insufficiency (in conjunction with mineralocorticoids, if applicable); acute adrenal insufficiency; preoperatively or 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; bilateral adrenalectomy; congenital adrenal hyperplasia; acute thyroiditis, nonsuppurative thyroiditis and thyroid crisis; hypercalcemia associated with cancer.

Shock
The principle of adjunctive corticosteroid therapy in shock is based on pharmacologic effects rather than a physiologic replacement.

Cerebral Edema (Increased Intracranial Pressure)
Clinical benefits of adjunctive corticosteroid therapy in cerebral edema are probably derived from the suppression of brain inflammation. Corticosteroids should not be considered a replacement for neurosurgery. They are of value in reduction or prevention of cerebral edema associated with surgical and other brain trauma, cerebrovascular accidents and primary or metastatic brain malignancies.

Renal Allograft Rejection Episodes
CELESTONE Injection has been found effective in the treatment of acute primary rejection and classical delayed rejection in conjunction with conventional therapy in the prevention of renal transplant rejection. Antepartum Use in the Prevention of Respiratory Distress Syndrome in Premature Infants
CELESTONE Injection is indicated as prophylactic treatment of hyaline membrane disease in premature infants when administered to mothers (prior to the 32nd week of gestation) before delivery.

Musculoskeletal Disorders
CELESTONE Injection may be administered as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in rheumatoid arthritis; osteoarthritis (post-traumatic or synovitis); psoriatic arthritis; ankylosing spondylitis; acute gouty arthritis; acute and subacute bursitis; acute rheumatic fever; fibrositis; epicondylitis; acute, nonspecific tenosynovitis; myositis; heloma.

CELESTONE Injection also may be useful in the treatment of cystic tumors of an aponeurosis or tendon (ganglia).
Collagen Disease
During an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus, acute rheumatic carditis, scleroderma and dermatomyositis.

Dermatologic Diseases
Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis; allergic eczema (chronic dermatitis); severe seborrheic dermatitis. Intraloseal administration is indicated for the treatment of keloids; localized hypertrophic, infiltrated, inflammatory lesions of lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis); discoid lupus erythematosus; necrobiotic lipoidic diabeticorum; alopecia areata.

Allergic States
Control of severe incapacitating allergic conditions intractable to adequate trials of conventional treatment, such as seasonal or perennial allergic rhinitis, nasal polyps, bronchial asthma (including status asthmaticus), contact dermatitis, atopic dermatitis (neurodermatitis), drug hypersensitivity, serum reactions; acute non-infectious laryngeal edema.

Ophthalmic Diseases
Severe, acute and chronic allergic and inflammatory processes involving the eyes and their adnexae, such as allergic conjunctivitis, keratitis, allergic corneal marginal ulcers, herpes zoster ophthalmicus, iritis, iridocyclitis, chorioretinitis, anterior segment inflammation, diffuse posterior uveitis and choroiditis, optic neuritis; sympathetic ophthalmia.

Respiratory Diseases
Symptomatic sarcoidosis; unmanageable Loeffler’s syndrome; berylliosis; fulminating or disseminated pulmonary tuberculosis when concurrently accompanied by appropriate antituberculous chemotherapy; aspiration pneumonitis.

Hematologic Disorders
Idiopathic and secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia; erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia; transfusion reactions.

Gastrointestinal Diseases
To tide the patient over a critical period of ulcerative colitis; regional enteritis.

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

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

Miscellaneous
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antitubercular chemotherapy; trichinosis with neurologic or myocardial involvement.

DOSAGE AND ADMINISTRATION
CELESTONE Injection can be used for IV, IM, intra-articular, intralesional or soft-tissue administration.

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

The initial adult dose of CELESTONE Injection may vary up to 8.0 mg betamethasone per day depending on the specific disease being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required.

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

The usual initial pediatric IM betamethasone dose varies from 0.02 to 0.125 mg per kg of body weight per day. Dosages for infants and children should be governed by the same considerations as adults rather than strict adherence to ratios indicated by age or body weight.
Although CELESTONE Injection may be administered by several routes, in emergency situations, the IV route is recommended. CELESTONE Injection may also be administered by IV drip in conjunction with either isotonic saline or dextrose solutions in the desired amount of solution. The addition of CELESTONE Injection to the solution for IV use should be made at the time of administration. Unused solutions should be refrigerated immediately and used within 24 hours.

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

Patient exposure to stressful situations unrelated to the disease under treatment may necessitate dosage increase of CELESTONE Injection. If the drug is to be discontinued after long-term therapy, the dosage should be decreased gradually.

**DOSING RECOMMENDATIONS FOR VARIOUS DISORDERS ARE AS FOLLOWS:**

**Cerebral Edema**
Objective and subjective evidence of improvement may occur within hours following administration of CELESTONE Injection, 2 mg to 4 mg betamethasone. Comatose patients may receive conventional dosages ranging from 2 mg to 4 mg four times a day.

**Renal Allograft Rejection Episodes**
At the first evidence and diagnosis of acute or delayed rejection, IV CELESTONE Injection is to be given by constant IV drip, the initial dose being 60 mg betamethasone during the first 24 hour period. There may be some minor variations in dosage according to individual circumstances.

**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 CELESTONE Injection, 4 to 6 mg betamethasone, be administered IM every 12 hours for 24 to 48 hours (2 to 4 doses) before the expected time of delivery. The necessity for initiating therapy at least 24 hours (or preferably 48 to 72 hours) before delivery is to allow sufficient time for the corticosteroid to exert its action and produce clinically detectable effects.

CELESTONE 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). In this situation the same dosage regimen should be used including the timing of the doses before delivery as recommended above.

**Musculoskeletal Disorders**
Recommended doses are dependent on joint size or site to be treated:

<table>
<thead>
<tr>
<th>SITE</th>
<th>Betamethasone (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Joints (hip)</td>
<td>2.0 mg to 4.0 mg</td>
</tr>
<tr>
<td>Small Joints</td>
<td>0.8 mg to 2.0 mg</td>
</tr>
<tr>
<td>Bursa</td>
<td>2.0 mg to 3.0 mg</td>
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<tr>
<td>Tendon Sheath</td>
<td>0.4 mg to 1.0 mg</td>
</tr>
<tr>
<td>Heloma (corn)</td>
<td>0.4 mg to 1.0 mg</td>
</tr>
<tr>
<td>Soft Tissue</td>
<td>2.0 mg to 6.0 mg</td>
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<tr>
<td>Ganglia</td>
<td>1.0 mg to 2.0 mg</td>
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**Transfusion Reactions**
For prevention of transfusion reactions, 1 or 2 ml CELESTONE Injection (4 or 8 mg betamethasone) should be administered IV immediately prior to the blood transfusion. The corticosteroid should not be mixed with the blood. With repeated transfusions, the same dose of CELESTONE Injection may be given up to a total of four times this dose for 24 hours, if necessary.

Subconjunctival Administration: Soluble corticosteroids have frequently been administered by subconjunctival injection for a number of corticosteroid responsive conditions of the eye. The usual dose of CELESTONE Injection is 0.5 ml (2 mg of betamethasone).

**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 Injection 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:** 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 hypertensive or shock-like reactions.

Additional adverse reactions related to parenteral corticosteroid therapy include rare instances
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 measure 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 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 reinstated. 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 psychopathic tendencies may be aggravated by corticosteroids.

Corticosteroids should be used with caution in: non-specific 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 physicians 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
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
CELESTONE Injection 4 mg/ml, 1 ml amp., 1 amp. pack

STORAGE
Stored not above 30°C. Keep the ampoules in the outer carton.

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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 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 corticosteroi or from deleterious effects of the basic or concomitant illnesses or resulting from drug interactions should be handled as appropriate.