Celestone® Chronodose®
BETAMETHASONE SODIUM PHOSPHATE AND
BETAMETHASONE ACETATE
Suspension for intramuscular, intra-articular and intralesional injection.

Shake well before use

NOT FOR INTRAVENOUS USE

1. DESCRIPTION
CELESTONE CHRONODOSE is a sterile aqueous suspension of betamethasone sodium phosphate and betamethasone acetate.

Each ml contains:
Betamethasone Acetate 3.000 mg
Betamethasone Sodium Phosphate* 3.945 mg
Preservative: Benzalkonium Chloride 0.2 mg
Equivalent to 3.0 mg Betamethasone

Inactive ingredients:
Disodium edetate, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dihydrate, benzalkonium chloride, water for Injection.

2. ACTIONS
Naturally occurring glucocorticoids (hydrocortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Betamethasone sodium phosphate, a soluble ester, provides prompt activity, while betamethasone acetate is only slightly soluble and affords sustained activity. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body’s immune responses to diverse stimuli.

3. INDICATIONS
When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, CELESTONE CHRONODOSE Suspension for intramuscular use is indicated as follows:
Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisol is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).
Acute adrenocortical insufficiency (hydrocortisone or cortisol is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used). Preoperatively and 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.
**Rheumatic disorders:** As adjunctive therapy for short term administration (to tide the patient over an acute episode or exacerbation) in: post-traumatic osteoarthritis; synovitis of osteoarthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy); acute and subacute bursitis; epicondylitis; acute nonspecific tenosynovitis; acute gouty arthritis; psoriatic arthritis; ankylosing spondylitis.

**Collagen disease:** During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; acute rheumatic carditis.

**Dermatologic diseases:** Pemphigus: severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; bullous dermatitis herpetiformis; severe seborrheic dermatitis; severe psoriasis; mycosis fungoides.

**Allergic states:** Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; seasonal or perennial allergic rhinitis; drug hypersensitivity reactions; urticarial transfusion reactions; acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

**Ophthalmic diseases:** Severe acute and chronic allergic and inflammatory processes involving the eye, such as: herpes zoster ophthalmicus; iritis; iridocyclitis; chorioretinitis; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia; anterior segment inflammation; allergic conjunctivitis; allergic corneal marginal ulcer; keratitis.

**Gastrointestinal diseases:** To tide the patient over a critical period of disease in: ulcerative colitis – (systemic therapy); regional enteritis – (systemic therapy).

**Respiratory diseases:** Symptomatic sarcoidosis; berylliosis; fulminating or disseminated pulmonary tuberculosis, when used concurrently with appropriate antituberculous chemotherapy; Loeffler’s syndrome not manageable by other means; aspiration pneumonitis.

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

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

**Edematous state:** To induce diuresis or remission of proteinuria in the nephritic 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 antituberculous chemotherapy. Trichinosis with neurologic myocardial involvement.

When the strength and dosage form of the drug lend the preparation to the treatment of the condition, the **intra-articular or soft tissue administration** of CELESTONE CHRONODOSE Suspension is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: synovitis of osteoarthritis; rheumatoid arthritis; acute and subacute bursitis; acute gouty arthritis; epicondylitis; acute nonspecific tenosynovitis; post-traumatic osteoarthritis.

When the strength and dosage form of the drug lend the preparation to the treatment of the condition, the **intra-lesional administration** of CELESTONE CHRONODOSE Suspension is indicated for: keloids, localized hypertrophic, inflammatory lesions of lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis); discoid lupus erythematosus; necrobiosis lipoidica diabetorum; alopecia areata. CELESTONE CHRONODOSE Suspension may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

**4. CONTRAINDICATIONS**

CELESTONE CHRONODOSE Suspension is contraindicated in systemic fungal infections. Patients hypersensitive to betamethasone sodium phosphate, betamethasone acetate, other corticosteroids, or to any component of this product.
5. WARNINGS
CELESTONE CHRONODOSE should not be administered intravenously.

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Dosage adjustments may be required with remission or exacerbation of the disease process and exposure of the patient to stress.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. Corticosteroids may mask some signs of infection and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

CELESTONE CHRONODOSE contains two betamethasone esters one of which, betamethasone sodium phosphate, disappears rapidly from the injection site. The potential for systemic effect produced by the soluble portion of CELESTONE CHRONODOSE should therefore be taken into account by the physician when using the drug. Average and large doses of cortisone or hydrocortisone 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 necessary. 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 who are on corticosteroids, especially in high doses, because of possible hazards of neurological complications and lack of antibody response. Immunization may take place in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison’s disease.

The use of CELESTONE CHRONODOSE Suspension 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 appropriate antituberculous 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.

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.

Usage during pregnancy, lactation or in women of child-bearing potential: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of child-bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.
6. PRECAUTIONS

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

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

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability, agitation or psychotic tendencies may be aggravated by corticosteroids.

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

Corticosteroids should be used with caution in: nonspecific ulcerative colitis as there may be a risk of impending perforation, abscess or other pyogenic infection diverticulitis; fresh intestinal anastomoses; active or latent gastrointestinal ulcer; erosive esophagitis; renal insufficiency; hypertension; osteoporosis and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Corticosteroids should be used with caution in patients with diabetes mellitus. Corticosteroids increase glucose levels and may require modification of dosing for insulin and other antihyperglycemic medications.

*The following additional precautions also apply for parenteral corticosteroids.*

**Intra-articular injection of a corticosteroid may produce systemic as well as local effects.**

Appropriate examination of any joint fluid present is necessary to exclude a septic process. A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided.

The slower rate of absorption by intramuscular administration should be recognized.

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

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.

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.

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

Results from a single, multicenter, randomized, controlled study with another corticosteroid, methylprednisolone hemisuccinate, showed an increase of early mortality (at 2 weeks) and late
mortality (at 6 months) in patients with cranial trauma who had received methylprednisolone, compared to placebo. The causes of mortality in the methylprednisolone group have not been established. Of note, this study excluded patients who were felt to have a clear indication for corticosteroids.

7. ADVERSE REACTIONS

**Cardiovascular:** hypertension; congestive heart failure.

**Fluid and electrolyte disturbances:** sodium retention; fluid retention; potassium loss; hypokalemic alkalosis.

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

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

**Dermatologic:** impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests; skin atrophy; reactions such as allergic dermatitis; urticaria; angionurotic edema.

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

**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 diabetics; suppression of fetal intrauterine growth.

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

**Metabolic:** negative nitrogen balance due to protein catabolism.

**Psychiatric:** euphoria; mood swings; depression; personality changes; insomnia.

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

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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL)

8. OVERDOSE

Treatment of acute overdose is administration of symptomatic therapy, as appropriate.

9. DRUG INTERACTIONS

**Amphotericin B injection and potassium-depleting agents:** When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., amphotericin-B, diuretics), patients should
be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

**Antibiotics:** Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

**Anticoagulants, oral:** Coadministration of corticosteroids and warfarin results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

**Antidiabetics:** Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

**Antitubercular drugs:** Serum concentrations of isoniazid may be decreased.

**Digitalis glycosides:** Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

**Estrogens, including oral contraceptives:** Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

**Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin):** Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

**Ketoconazole:** Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

**Nonsteroidal anti-inflammatory agents (NSAIDS):** Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

**10. INTERFERENCE WITH LABORATORY TESTS**

Corticosteroids may suppress reactions to skin tests.

**11. DOSAGE AND ADMINISTRATION**

The initial dosage of CELESTONE CHRONODOSE Suspension may vary from 0.5 to 9.0 mg per day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. Usually the parenteral dosage ranges are one-third to one-half the oral dose given every 12 hours. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, CELESTONE CHRONODOSE Suspension should be discontinued and the patient transferred to other appropriate therapy. It should be emphasized that dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient’s individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the
dosage of CELESTONE CHRONODOSE Suspension for a period of time consistent with the patient’s condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

If coadministration of a local anesthetic is desired, CELESTONE CHRONODOSE Suspension may be mixed with 1% or 2% lidocaine hydrochloride, using the formulations which do not contain parabens. Similar local anesthetics may also be used. Diluents containing methylparaben, propylparaben, phenol, etc., should be avoided since these compounds may cause flocculation of the steroid. The required dose of CELESTONE CHRONODOSE Suspension is first withdrawn from the vial into the syringe. The local anesthetic is then drawn in, and the syringe shaken briefly. **Do not inject local anesthetics into vial of CELESTONE CHRONODOSE Suspension.**

*Bursitis. Tenosynovitis, Peritendinitis.* In acute subdeltoid, subacromial, olecranon, and prepatellar bursitis, one intrabursal injection of 1.0 ml CELESTONE CHRONODOSE Suspension can relieve pain and restore full range of movement. Several intrabursal injections of corticosteroids are usually required in recurrent acute bursitis and in acute exacerbations of chronic bursitis. Partial relief of pain and some increase in mobility can be expected in both conditions after one or two injections. Chronic bursitis may be treated with reduced dosage once the acute condition is controlled. In tenosynovitis and tendonitis, there or four local injections at intervals of one to two weeks between injections are given in most cases. Injections should be made into the affected tendon sheaths rather than into tendons themselves. In ganglions of joint capsules and tendon sheaths, injections of 0.5 ml directly into the ganglion cysts has produced marked reduction in the size of the lesions.

*Rheumatoid arthritis and osteoarthritis.* Following intra-articular administration of 0.5 to 2.0 ml of CELESTONE CHRONODOSE Suspension, relief of pain, soreness, and stiffness may be experienced. Duration of relief varies widely in both diseases.

**Intra-articular Injection -** CELESTONE CHRONODOSE Suspension is well tolerated in joints and periarticular tissues. There is virtually no pain on injection, and the “secondary flare” that sometimes occurs a few hours after intra-articular injection of corticosteroids has not been reported with CELESTONE CHRONODOSE Suspension. Using sterile technique, a 20- to 24-gauge needle on an empty syringe 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 a syringe containing CELESTONE CHRONODOSE Suspension and injection is then made into the joint.

**Recommended Doses for Intra-articular Injection**

<table>
<thead>
<tr>
<th>Size of joint</th>
<th>Location</th>
<th>Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Large</td>
<td>Hip</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Large</td>
<td>Knee, Ankle, Shoulder</td>
<td>1.0</td>
</tr>
<tr>
<td>Medium</td>
<td>Elbow, Wrist</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Metacarpophalangeal, Interphalangeal)</td>
<td>Hand, Chest</td>
<td>0.25-0.5</td>
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<tr>
<td>(Sternoclavicular)</td>
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</tbody>
</table>

A portion of the administered dose of CELESTONE CHRONODOSE Suspension is absorbed systemically following intra-articular injection. In patients being treated concomitantly with oral or parenteral corticosteroids, especially those receiving large doses, the systemic absorption of the drug should be considered in determining intra-articular dosage.
Dermatologic conditions: In intralesional treatment, 0.2 ml/sq. cm. of CELESTONE CHRONODOSE Suspension injected intradermally (not subcutaneously) using a tuberculin syringe with a 25-gauge, ½-inch needle. Care should be taken to deposit a uniform depot of medication intradermally. A total of no more than 1.0 ml at weekly intervals is recommended.

Disorders of the foot: A tuberculin syringe with a 25-gauge, ¾-inch needle is suitable for most injections into the foot. The following doses are recommended at intervals of three days to a week.

CELESTONE CHRONODOSE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Suspension Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursitis</td>
<td></td>
</tr>
<tr>
<td>Under heloma durum or heloma molle</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>Under calcaneal spur</td>
<td>0.5</td>
</tr>
<tr>
<td>Over hallux rigidus or digiti quinti varus</td>
<td>0.5</td>
</tr>
<tr>
<td>Tenosynovitis, periostitis of cuboid</td>
<td>0.5</td>
</tr>
<tr>
<td>Acute gouty arthritis</td>
<td>0.5-1.0</td>
</tr>
</tbody>
</table>

12. HOW SUPPLIED
Box of 1 ampoule of 1 ml.

13. STORAGE AND HANDELING
Shake well before using.
Store below 25ºC. Do not freeze.

14. MANUFACTURER
Schering-Plough Labo N.V., Heist-op-den-berg, Belgium

15. LICENSE HOLDER
Merck Sharp & Dohme (Israel-1996) Company Ltd.,
P.O.Box 7121, Petah-Tikva 49170.

16. LICENSE NUMBER
131.43.23009.01

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