CELESTONE® CHRONODOSE INJECTION
PRODUCT INFORMATION

NAME OF THE MEDICINE

Betamethasone injection (Betamethasone acetate and Betamethasone sodium phosphate)

Chemical structure:

\[
\text{betamethasone acetate} \\
9\text{-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4diene-21-yl acetate)}
\]
Molecular formula: \(\text{C}_{24}\text{H}_{31}\text{FO}_{6}\)  \(\text{MW:434.5}\)  \(\text{CAS registry number: 987-24-6}\)

\[
\text{betamethasone sodium phosphate} \\
9\text{-fluoro-11β,17-dihydroxy-16β-methyl-3,20-dioxopregna-1,4diene-21-yl disodium phosphate}
\]
Molecular formula: \(\text{C}_{22}\text{H}_{28}\text{FNa}_{2}\text{O}_{8}\)  \(\text{MW:516.4}\)  \(\text{CAS registry number: 151-73-5}\)

DESCRIPTION

Each mL of Celestone Chronodose Injection contains betamethasone 5.7 mg, as betamethasone sodium phosphate 3.9 mg (in solution) and betamethasone acetate 3 mg (in suspension) in an aqueous vehicle. It also contains benzalkonium chloride, disodium edetate, dibasic anhydrous sodium phosphate, monobasic sodium phosphate and water for injections.

PHARMACOLOGY

Celestone Chronodose is an injectable preparation containing both soluble and slightly soluble esters of betamethasone that provides anti-inflammatory, anti-rheumatic and anti-allergic effects in the treatment of corticosteroid-responsive disorders.

Prompt therapeutic activity in conditions responsive to corticosteroids is initiated by betamethasone sodium phosphate, a soluble ester that is absorbed quickly into tissues after injection.
Sustained activity is provided by betamethasone acetate, which is only slightly soluble and affords a repository for slow absorption.

The combined rapid and depot actions of these forms of betamethasone facilitate rapid control as well as steady maintenance of corticosteroid effects.

INDICATIONS

Celestone Chronodose is indicated in the treatment of both severe and moderate conditions, in acute and chronic self-limiting diseases responsive to systemic corticosteroid therapy, especially in patients for whom treatment with oral corticosteroid medication is not feasible.

Representative conditions:

**Rheumatic disorders:** Rheumatoid arthritis, acute and subacute bursitis, epicondylitis, acute non-specific tenosynovitis, myositis, fibrositis, tendinitis, psoriatic arthritis.

**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 drug and insect bites.

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

**Antepartum use in the prevention of respiratory distress syndrome in premature infants** when it is deemed necessary to induce labour prior to the thirty-second week of gestation or when premature birth before the thirty-second week of gestation becomes inevitable because of obstetric complication.

Celestone Chronodose Injection should also be considered for prophylactic treatment if the foetus is known to have a low lecithin/sphingomyelin ratio (or decreased foam stability test on amniotic fluid).

CONTRAINDICATIONS

As with other corticosteroids, Celestone Chronodose Injection is contraindicated in systemic fungal infections and in patients hypersensitive to betamethasone sodium phosphate, betamethasone acetate, other corticosteroids or to any component of this product. Corticosteroids should not be injected into unstable joints, infected areas or intervertebral spaces. Celestone Chronodose Injection is not recommended for epidural administration.

Relative contraindications are osteoporosis, marked emotional instability, peptic ulcer, tuberculosis, acute or chronic infections, ocular Herpes simplex, primary glaucoma, diverticulitis, recent intestinal anastomosis, Cushing’s syndrome, renal insufficiency, hypertension, thromboembolic tendencies, diabetes mellitus and myasthenia gravis.

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

Celestone Chronodose Injection should not be administered intravenously. Strict aseptic technique is mandatory. Subcutaneous injection should be avoided.

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. (See CONTRAINDICATIONS)

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

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

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.

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 minimised by gradual reduction of dosage. This type of 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, the dosage may have to be increased.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticosteroid should be administered concurrently. In certain conditions ordinarily considered contraindications to corticosteroid therapy, the physician must weigh anticipated clinical improvement against the possibility of undesirable corticosteroid effects.

Corticosteroids may mask the signs of infection and enhance the dissemination of an infecting organism. Hence, patients receiving corticosteroids should be watched for evidence of intercurrent infection. Should infection occur, vigorous, appropriate anti-infective therapy should be initiated. Abrupt withdrawal of corticosteroids should be avoided.

Celestone Chronodose Injection should not be administered to patients with an acute or chronic infection unless the condition is severe and unless appropriate anti-infective agents are administered concurrently. When corticosteroids are used, decreased resistance and inability to localise infection may occur.

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 anti-microbial therapy should be instituted.
While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunisation 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, immunisation procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g. for Addison's 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 anti-tuberculous 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 rifampicin 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.

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

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

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.

Celestone Chronodose Injection should be administered intramuscularly with caution to patients with idiopathic thrombocytopenic purpura.

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

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.

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.

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.

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.

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

Results from a single, multicentre, randomised, 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.

**Use in Pregnancy (Category C)**

The use of corticosteroids in pregnancy or in women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and foetus.

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.

Since use of prophylactic corticosteroids beyond the 32nd week of gestation is still controversial, the physician should weigh the benefits against the potential hazards to the mother and the foetus when using corticosteroids beyond this period of gestation.

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations) and abortion. These findings do not seem to be relevant to humans. Reduced placental and birth weight have been recorded in animals and humans after long-term treatment. Since the possibility of suppression of the adrenal cortex in the newborn baby after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the foetus when prescribing these drugs. The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the foetus or the newborn infant.

Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

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

Since 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 labour and delivery for any indication of adrenal insufficiency because of the stresses associated with childbirth.

Use in lactation

The drug is excreted in breast milk and may be harmful to young children because it could suppress growth or cause other adverse effects such as hypo-adrenalism. Potential benefits to the mother should outweigh these possible hazards to the infant.

Paediatric use

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.

Effect on laboratory tests

Corticosteroids may affect the nitro-blue tetrazolium test for bacterial infection and produce false negative results.

INTERACTIONS WITH OTHER MEDICINES

Plasma levels of salicylates may be reduced. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

Concurrent use of phenobarbitone, phenytoin, rifampicin or ephedrine may enhance the metabolism of corticosteroids, reducing their therapeutic effects.

The hyperglycaemic effect of betamethasone may offset the hypoglycaemic effect of oral antidiabetic drugs. Dosage adjustments of an anti-diabetic drug may be necessary when corticosteroids are given to diabetics.

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

Concurrent use of corticosteroids with potassium-depleting diuretics may enhance hypokalaemia. Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalaemia. 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 anti-coagulants may increase or decrease the anti-coagulant 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.

Concomitant glucocorticosteroid therapy may inhibit the response to somatotropin. Doses of betamethasone in excess of 0.3 to 0.45 mg per m² of body surface per day should be avoided during the administration of somatotropin.

**ADVERSE EFFECTS**

Adverse reactions to Celestone Chronodose Injection relate both to dose and to duration of therapy. These reactions can usually be reversed or minimised by a reduction in dosage; this is generally preferable to withdrawal of drug treatment.

Adverse reactions have been the same as those reported to other corticosteroids: fluid and electrolyte, musculoskeletal, gastrointestinal, dermatological, neurological, endocrine, ophthalmic, metabolic and psychiatric disturbances.

*Fluid and electrolyte disturbances*: sodium retention, potassium loss, hypokalaemic 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 haemorrhage; pancreatitis; abdominal distention; ulcerative oesophagitis.

*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 oedema.

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

*Endocrine*: menstrual irregularities; development of cushingoid state; suppression of foetal intrauterine and 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 hypoglycaemic 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; post-injection flare (following intra-articular use); charcot-like arthropathy.

**DOSAGE AND ADMINISTRATION**

**Dosage must be adjusted to the specific requirements of the patient according to the severity of the condition, the response obtained, and the patient’s tolerance to the corticosteroid.**

Recommended routes of administration are:

1. Intramuscular injection in allergic, dermatological, 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 muscle such as fibrositis and myositis.

3. Intra-articular and periarticular injection in rheumatoid arthritis and osteoarthritis.

4. Intralesional injections in various dermatological conditions.

**Systemic administration:** Treatment of conditions requiring systemic corticoid effects can be carefully controlled by intramuscular injection 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 corticoid effects.

Treatment is initiated with an intramuscular injection of 1 mL in most conditions and repeated weekly, or more often, if necessary. In severe illness, such as status asthmaticus or disseminated lupus erythematosus, 2 mL might be required initially.

In the antepartum use in the prevention of respiratory distress syndrome in premature infants and in the prophylactic treatment of the foetus known to have a low lecithin/sphingomyelin ratio (or decreased foam stability tests on amniotic fluid), it is recommended that 2 mL 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.

**Local administration.** If co-administration is desired, Celestone Chronodose Injection may be mixed (in the syringe not the ampoule) with 1% or 2% lignocaine hydrochloride, procaine hydrochloride, or similar local anaesthetics, using formulations which do not contain hydroxybenzoates (parabens). Anaesthetics containing methyl hydroxybenzoate, propyl hydroxybenzoate, phenol, etc. should be avoided. The required dose is first withdrawn from the ampoule into the syringe. The local anaesthetic is then drawn into the syringe and then should be shaken briefly.

In bursitis (subdeltoid, subacromial and prepatellar) an intrabursal injection of 1 mL may relieve pain and may restore 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 tendinitis, myositis, fibrositis, tenosynovitis, peritendinitis, 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. Dosages range 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 lasts usually from 1 to 4 or more weeks. Using a 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.

A portion of the administered dose of Celestone Chronodose Injection is absorbed systemically following intra-articular injection. Therefore, in patients being treated concomitantly with oral or parenteral corticosteroids, especially those receiving large doses, the systemic absorption of the drug administered intra-articularly should be considered.

In intralesional treatment, 0.2 mL/cm² of Celestone Chronodose Injection is injected intradermally (not subcutaneously) using a tuberculin syringe with a 25 gauge, 1.27 cm needle. Care should be taken to deposit a uniform depot of medication intradermally. A total of not more than 1 mL at weekly intervals is recommended.

OVERDOSAGE

A single overdose of a corticosteroid would not be expected to produce acute symptoms. Hypercorticoid effects are not anticipated unless there has been repeated administration of high doses.

Symptoms: Systemic effects of chronic overdosage with steroids include effects on sodium and water retention, increased appetite, mobilisation of calcium and phosphorus with osteoporosis, nitrogen depletion, hyperglycaemia, effects on tissue repair, increased susceptibility to infection, adrenal insufficiency, adrenal cortex hyperactivity, mental and neurological disturbances and muscular weakness.

Treatment: In case of an acute overdose, maintain adequate fluid intake and monitor electrolytes in serum and urine, with particular attention to sodium and potassium balance. In case of chronic toxicity, slowly withdraw drug. Treat electrolyte imbalance if necessary.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.
PRESENTATION AND STORAGE CONDITIONS

Injection, suspension in flint glass (Type I) ampoule with rubber stopper
Ampoules, 1 mL: 5s, 2s

Protect ampoules from light.
Store below 25°C.

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1-Building A, 26 Talavera Road,
Macquarie Park, NSW 2113Australia

Merck Sharp & Dohme (New Zealand) Ltd
P O Box 99 851
Newmarket
Auckland 1149
New Zealand

POISON SCHEDULE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS
8 October 1991

DATE OF MOST RECENT AMENDMENT: 11 February 2015