1. PRODUCT NAME

CELESTONE® CHRONODOSE®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Celestone Chronodose Injection is a sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate. 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Celestone Chronodose Injection is recommended in the therapy of both severe and moderate diseases, in acute and chronic self-limiting diseases responsive to systemic corticosteroid therapy, 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.

Representative conditions:
Rheumatic disorders.
Rheumatoid arthritis, acute and subacute bursitis, epicondylitis, acute nonspecific tenosynovitis, myositis, fibrositis, tendonitis, 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 drugs 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).

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

4.2 Dose and method of administration

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

After a favourable 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.

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 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. Intralesional injections in various dermatological conditions.

Systemic administration
Treatment of conditions requiring systemic corticosteroid effects can be carefully controlled by intramuscular injection. Its rapid and prolonged action makes 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 of Celestone Chronodose 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.

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 parabens (hydroxybenzoates). Anaesthetics containing methyl paraben, propyl paraben, phenol, etc. should be avoided. The required dose is first withdrawn from the ampoule into the syringe. The local anaesthetic 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 1mL 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.

In intralesional treatment, 0.2 mL/cm^2 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 should not exceed 1 mL per week.

4.3 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 (see Section 6.1 List of Excipients).

Celestone Chronodose Injection is not recommended for epidural administration.

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

4.4 Special warnings and precautions for use

Celestone Chronodose Injection is not for intravenous or subcutaneous use.

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, myasthenia gravis.

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.

Rare instances of anaphylactoid/anaphylactic reactions with a possibility of shock have occurred in patients receiving parenteral corticosteroid therapy. Appropriate precautionary measures should be taken with patients who have a history of allergic reactions to corticosteroids.

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 foetus when using corticosteroids beyond this gestational period.

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 anti-microbial 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.

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.

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

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 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, the 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: 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.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use in Children
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.

4.5 Interaction with other medicines and other forms of interaction

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.

Anticoagulants, Oral
Concurrent use of corticosteroids with coumarin-type anti-coagulants may increase or decrease the anti-coagulant effects, possibly requiring adjustment in dosage.

Antidiabetics
Dosage adjustments of an anti-diabetic drug may be necessary when corticosteroids are given to diabetics.

Oestrogens, Including Oral Contraceptives
Patients receiving both a corticosteroid and an oestrogen should be observed for excessive corticosteroid effects.

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

Interactions with Strong CYP3A4 Inhibitors
Corticosteroids (including betamethasone) are metabolized by CYP 3A4.

Coadministration with other strong CYP3A4 inhibitors, (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased exposures of corticosteroids and therefore the potential for increased risk of systemic corticosteroid side effects.

Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Nonsteroidal Anti-Inflammatory Agents (NSAIDs)
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. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Somatotropin
Concomitant glucocorticosteroid therapy may inhibit the response to somatotropin.

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

4.6 Fertility, pregnancy and lactation

Use in pregnancy
Since controlled human reproduction studies have not been conducted with corticosteroids, the use of these drugs at any time during 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.

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 foetus 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 corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism. When mothers were given betamethasone injections prenatally, 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
Corticosteroids cross the placenta barrier and appear in the breast milk of breastfeeding mothers. Because of the potential for unwanted adverse effects from Celestone Chronodose Injection in breastfeeding infants, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on fertility
Corticosteroids may alter the motility and number of spermatozoa in some patients

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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 minimised by a reduction in dosage; this is generally preferable to withdrawal of drug treatment.

Cardiovascular
Congestive heart failure in susceptible patients, hypertension.

Fluid and electrolyte disturbances
Sodium retention, potassium loss, hypokalemic alkalosis, fluid retention.

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.

Dermatological
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, angioedema.

Neurological
Convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache.

Endocrine
Menstrual irregularities, development of cushingoid state, suppression of foetal 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 hypoglycaemic agents in diabetics.

Ophthalmic
Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, vision blurred.

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) and charcot-like arthropathy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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 anti-coagulants 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. In case of chronic toxicity, slowly withdraw drug. Treat electrolyte imbalance if necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: corticosteroid for systemic use, glucocorticoid, ATC code: H02A B01.

Celestone Chronodose 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.

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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

No Preclinical safety data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium phosphate
sodium phosphate monobasic
disodium edetate
benzalkonium chloride
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 25°C. Protect ampoules from light.

6.5 Nature and contents of container

Box of 5 ampoules (1 mL)

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Organon New Zealand Limited
PO Box 99 851
Newmarket
Auckland 1149
Tel: 0800 111 700

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

1 December 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Amend sponsor details due to transfer of sponsorship