SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Celestone Chronodose

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 3.945 mg betamethasone sodium phosphate and 3 mg betamethasone acetate.

Excipients with known effect:
1 ml ampoule contains 0.2 mg benzalkonium chloride which is equivalent to 0.2 mg/ml.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection for intramuscular, intra-articular, intralesional, administration and injection in soft tissue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The product is indicated in the management of conditions known to be responsive to corticosteroid therapy.

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 cortisone 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 cortisone 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. Congenital adrenal hyperplasia. Nonsuppurative thyroiditis. Hypercalcemia associated with cancer.
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. Erythro-blastopenia (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 diabeticorum; alopecia areata.
Celestone Chronodose suspension may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

4.2 Posology and method of 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 ampule into the syringe. The local anesthetic is then drawn in, and the syringe shaken briefly.
Do not inject local anesthetics into ampule 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

Size of joint	Location	Dose (ml)
Very Large	Hip	1.0-2.0
Large	Knee, Ankle, Shoulder	1.0
Medium	Elbow, Wrist	0.5-1.0
Small (Metacarpophalangeal, Interphalangeal) (Sternoclavicular)	Hand, Chest	0.25-0.5

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

Diagnosis	**Suspension Dose (ml)**
Bursitis	
Under heloma durum or heloma molle	0.25-0.5
Under calcaneal spur	0.5
Over hallux rigidus or digiti quinti varus	0.5
Tenosynovitis, periostitis of cuboid	0.5
Acute gouty arthritis	0.5-1.0

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to corticosteroids;
- Systemic fungal infections.

Celestone Chronodose cannot be used for intrathecal administration.

4.4 Special warnings and precautions for use

Celestone Chronodose cannot be used for intravenous or subcutaneous administration.

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.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

ANTISEPTIC TECHNIQUES ARE NECESSARY.

Celestone Chronodose contains two betamethasone esters, one of which, betamethasone sodium phosphate, disappears rapidly from the injection site. Therefore, when using this product, the physician must take into account that this soluble portion of Celestone Chronodose may have a systemic effect.

Corticosteroids are not indicated to treat hyaline membranes after birth. For the prophylactic treatment of hyaline membrane disease in premature infants, do not administer

corticosteroids to pregnant women with pre-eclampsia or eclampsia or with signs of placental lesions.

Intramuscular injection of corticosteroids should be performed deep in large muscle masses to avoid local tissue atrophy.

Celestone Chronodose intramuscular injection should be administered with caution in patients with idiopathic thrombocytopenic purpura.

The injection of corticosteroids in soft tissue, and their intralesional or intra-articular injection may induce systemic as well as local effects.

It is essential to examine any liquid that may be present in the joint, in order to exclude a septic process. Avoid local injection into a previously infected joint. A net increase in pain and local swelling, further decrease in joint mobility, fever and malaise should raise the question of septic arthritis. If the diagnosis of infection is confirmed, appropriate antimicrobial treatment must be initiated.

Do not inject corticosteroids in unstable joints, infected areas or intervertebral spaces. Repeated injections into osteoarthritis-affected joints can aggravate the destruction of the joint. Avoid injecting corticosteroids directly into tendons because tendon ruptures have been seen to occur subsequently.

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.

During prolonged corticosteroid therapy, consider switching from parenteral to oral administration after weighing the potential benefits and risks.

Glucocorticoids may mask certain signs of infection, and new infections may appear during their use. A decrease in resistance and difficulty in localizing the infection can be observed when using glucocorticoids.

Prolonged use can lead to posterior subcapsular cataract (especially in children) or to glaucoma, which can damage the optic nerves, and may exacerbate secondary ocular infections due to fungi or viruses. In case of prolonged treatment (over 6 weeks), it is necessary to have regular ophthalmological examinations.

Average and large doses of corticosteroids can induce hypertension, fluid retention and increased potassium excretion. A low sodium diet and potassium supplements may be considered. All corticosteroids increase calcium excretion.

PATIENTS ON CORTICOTHERAPY CANNOT RECEIVE THE FOLLOWING TYPES OF TREATMENT:
- SMALLPOX VACCINATION;
- OTHER METHODS OF IMMUNIZATION (ESPECIALLY AT HIGH DOSE) BECAUSE OF THE RISK OF NEUROLOGICAL COMPLICATIONS AND INADEQUATE ANTIBODY RESPONSE.

However, patients receiving corticosteroids as replacement therapy, may be immunized (e.g., Addison's disease).
Patients, especially children, receiving immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles.

In the case of active tuberculosis, corticosteroids should be limited to cases of fulminating or disseminated tuberculosis, where corticosteroids are used in combination with a suitable anti-tubercular treatment regimen.

If corticosteroids are indicated in patients with latent tuberculosis or reacting to tuberculin, strict monitoring is necessary, because it can produce a reactivation of the disease. During prolonged corticosteroid therapy, patients should receive chemoprophylaxis. If using rifampicin in a chemoprophylaxis program, its enhancing effect on the metabolic hepatic clearance of corticosteroids must be remembered; it may be necessary to adjust the dose of the corticosteroid.

Secondary adrenocortical insufficiency induced by the medicinal product can be minimized by gradual reduction of the dosage. This relative insufficiency may last for several months after discontinuation of therapy; if a state of stress is observed during this period, a new hormonal treatment must be initiated. Since mineralocorticoid secretion may be impaired, it is necessary to provide simultaneous administration of a mineralocorticoid and/or salt.

Glucocorticoids exert a greater effect in hypothyroidism or cirrhosis.

Given the risk of corneal perforation, glucocorticoids should be administered with caution in patients with ocular herpes simplex.

Emotional instability and existing psychotic tendencies may be aggravated by corticosteroids.

Caution is advised in:
Nonspecific ulcerative colitis - Impending perforation of abscesses and other pyogenic infections - Diverticulitis - Intestinal anastomosis - Gastro-duodenal ulcer - Renal insufficiency - Hypertension - Osteoporosis - Myasthenia gravis.

As corticosteroids can disrupt the growth of infants and children and inhibit the endogenous production of corticosteroids, it is important to monitor their growth and development carefully during prolonged treatment.

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

Cases of tendon rupture have been reported when corticosteroids and fluoroquinolones are administered separately. Therefore, simultaneous administration may increase the risk.

Special monitoring of the patient is required in the following situations:
tuberculosis, ocular herpes simplex, glaucoma, acute psychosis, active or latent gastric ulcer, Cushing's syndrome, renal insufficiency, hypertension, osteoporosis, diabetes, psychotic tendencies,
viral and bacterial infections, heart failure, difficult-to-treat epilepsy, growth failure, diverticulitis, recent intestinal anastomoses, thromboembolism or thrombophlebitis tendencies, myasthenia gravis, pregnancy.

Visual disturbance

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.

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.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

Benzalkonium chloride
Celestone Chronodose contains benzalkonium chloride, which can cause irritation and skin reactions.
This medicine contains 0.2 mg benzalkonium chloride in each 1 ml ampoule which is equivalent to 0.2 mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products:
Combination with phenobarbital, rifampin, phenytoin or ephedrine may increase the metabolism of corticosteroids, resulting in a decrease in therapeutic effect.

Patients who simultaneously receive a corticosteroid and an estrogen must be monitored for excessive corticosteroid effects.

The simultaneous administration of corticosteroids and cardiac glycosides may increase the risk of arrhythmias or digitalis toxicity related to hypokalemia. Often, patients using cardiac glycosides also take diuretics which induce potassium depletion; in this case, it is essential to conduct potassium level determinations. Corticosteroids may aggravate the potassium depletion caused by amphotericin B. In all patients taking one of these medication combinations, serum electrolytes, particularly serum potassium, should be closely monitored.

The simultaneous use of corticosteroids and coumarin-type anticoagulants may increase or decrease the effects of anticoagulants, which may require a dosage adjustment.

Corticosteroids may decrease the concentration of blood levels of salicylates. In hypoprothrombinemia, caution should be observed when using acetylsalicylic acid during corticotherapy.

The combination with non-steroidal anti-inflammatories or alcohol can lead to an increased risk of developing a gastrointestinal ulcer or worsening of an existing ulcer.

In diabetics, it is sometimes necessary to adjust the dose of oral antidiabetic agents or insulin, given the intrinsic hyperglycemic effect of glucocorticoids.

Combination with somatotropin may inhibit the response to this hormone. Betamethasone doses greater than 300-450 µg (0.3 to 0.45 mg) per m^2 of body surface area per day should be avoided during administration of somatotropin.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Other forms of interactions
Interactions with laboratory tests

Corticosteroids may influence the nitro blue tetrazolium reduction test and produce false negative results.

4.6 Fertility, pregnancy and lactation

Pregnancy
Some animal experiments have shown that high doses of glucocorticoids administered during pregnancy can be the cause of fetal defects.
Given the lack of adequate teratogenic studies in humans, glucocorticoids can only be administered during pregnancy, breast-feeding and in women of fertile age after having thoroughly evaluated the health benefits and potential risks of these medications for the mother and the embryo or fetus.

Published data show that the prophylactic use of corticosteroids after the 32nd week of pregnancy is still controversial. Therefore, the physician should weigh the benefits and potential risks for the mother and fetus when using corticosteroids after the 32nd week of pregnancy.

Corticosteroids are not indicated to treat hyaline membranes after birth.

In prophylactic treatment of hyaline membrane disease in premature infants, do not administer corticosteroids to pregnant women with preeclampsia or eclampsia or with signs of placental lesions.

Newborns whose mothers received substantial doses of glucocorticoids during pregnancy should be subject to a careful examination for possible signs of adrenal insufficiency or, more rarely, congenital cataract.

Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of betamethasone to women at risk for late preterm delivery.

Breastfeeding
Corticosteroids are excreted in breast milk.

Given that Celestone Chronodose may induce undesirable side effects in breast-fed infants, a decision must be made whether to stop breast-feeding or stop the medicine, taking into consideration the importance of the medicinal product for the mother.

Women who received corticosteroids during pregnancy should be monitored during and after contractions and during childbirth to detect adrenal insufficiency due to the stress caused by birth.

4.7 Effects on ability to drive and use machines

Although vision problems are rare side effects, patients who drive vehicles or machinery must be informed of that.

4.8 Undesirable effects

Adverse reactions observed with Celestone Chronodose, which are the same as those mentioned for other corticosteroids, are related to both dose and duration of treatment.

Among the side effects of corticosteroids in general, the following effects are to be particularly noted:

Fluid and electrolyte disorders
Sodium retention - Potassium loss - Hypokalemic alkalosis - Fluid retention - Congestive heart failure in susceptible patients - Hypertension

Musculoskeletal
Muscle weakness - Loss of muscle mass - Osteoporosis - Vertebral compression fractures - Aseptic necrosis - Tendon rupture - Steroid myopathy - Pathological fracture - Instability of joints - Aggravation of myasthenic symptoms in myasthenia gravis

Gastrointestinal
Hiccups - Peptic ulcer with possible perforation and hemorrhage - Pancreatitis - Abdominal distension - Ulcerative esophagitis

Dermatological
Skin atrophy - Defective healing - Thin and fragile skin - Petechiae and bruises - Hypersensitivity reactions - Allergic dermatitis - Angioneurotic edema

Neurological
Seizures - Increased intracranial pressure (pseudotumor cerebri) - Vertigo - Headache

Endocrine
Irregular menstruation - Cushingoid state - Growth inhibition in children - Inhibition of pituitary-adrenal axis - Decreased glucose tolerance - Manifestations of latent diabetes mellitus - Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic
Posterior subcapsular cataract - Increased intraocular pressure - Glaucoma - Exophthalmos- Vision blurred (see also section 4.4)

Metabolic
Negative nitrogen balance due to protein catabolism - Lipomatosis - Weight Gain

Psychiatric
Euphoria - Unstable mood - Personality disorders and severe depression with manifestation of psychotic phenomena - Insomnia

Other
Anaphylactic or allergic reactions - Some hypotensive reactions or reactions related to shock may occur

THE FOLLOWING ADVERSE REACTIONS MAY BE OBSERVED DURING PARENTERAL CORTICOTHERAPY:
Rare cases of blindness associated with intralesional treatment of the face and head - Hyperpigmentation or hypopigmentation - Subcutaneous and cutaneous atrophy - Sterile abscess - Post-injection exacerbation (after intra-articular use) - Charcot arthropathy

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any

suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Symptoms
Acute overdosage of glucocorticoids, including betamethasone, is not life-threatening.

Except in extreme doses, it is unlikely that a few days of glucocorticoid overdose will have negative consequences in the absence of specific contraindications such as diabetes, glaucoma, active peptic ulcer, or when administering medications such as digitalis, coumarin anticoagulants or potassium-sparing diuretics.
Chronic overdose can induce iatrogenic Cushing's disease (moon face, impotence, amenorrhea).

Measures
The complications resulting from the metabolic effects of corticosteroids, or the deleterious effects of the main disease or concomitant diseases, as well as the complications resulting from medication interactions, should be treated appropriately. It is necessary to ensure adequate fluid intake and monitor electrolytes in the serum and urine, paying particular attention to the sodium and potassium balance. If necessary, the electrolyte imbalance must be treated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Betamethasone is a synthetic glucocorticoid (9 alpha-fluoro-16 beta-methylprednisolone). Betamethasone has strong anti-inflammatory, immunosuppressive and anti-allergic activity.

Betamethasone has no clinically significant mineralocorticoid effect.

Glucocorticoids diffuse across cell membranes and form complexes with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin) and stimulate the transcription of messenger RNA and protein synthesis of various enzymes. These are finally responsible for the effects observed in systemic glucocorticoid use. In addition to their significant effect on inflammatory and immune processes, glucocorticoids also influence the metabolism of carbohydrates, proteins and lipids. Finally, they also have an effect on the cardiovascular system, skeletal muscles and the central nervous system.

Effect on inflammatory and immune processes
The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids account for a very substantial part of their therapeutic applications. The main aspects of these properties are: reduction in the number of immuno-active cells at the inflammatory site, reduced vasodilation, stabilization of lysosomal membranes, inhibition of phagocytosis, reduced production of prostaglandins and related substances.

The anti-inflammatory activity is about 25 times greater than that of hydrocortisone, and 8 to 10 times greater than that of prednisolone (on a weight basis). 100 mg of hydrocortisone is equivalent to 4 mg of betamethasone.

Effect on the metabolism of carbohydrates and proteins
Glucocorticoids stimulate protein catabolism. In the liver, the released amino acids are converted into glucose and glycogen by the process of gluconeogenesis. Glucose uptake in peripheral tissues decreases, which leads to hyperglycemia and glucosuria, especially in patients with a diabetic predisposition.

Effect on lipid metabolism
Glucocorticoids have lipolytic activity. This lipolysis is more pronounced in the limbs. They also have a lipogenic effect that occurs mainly in the trunk, neck and head. As a whole, these effects lead to a redistribution of fat deposits.

The maximum pharmacological activity of corticosteroids appears later than the peak serum levels, suggesting that the majority of effects of these medications are not based on direct activity of the medicinal product, but on the modification of enzyme activity.

5.2 Pharmacokinetic properties

Betamethasone disodium phosphate and betamethasone acetate are resorbed from the injection site and induce therapeutic effects and other pharmacological effects, both locally and systemically.

Betamethasone disodium phosphate is highly soluble in water and is metabolized in the body into betamethasone, the biologically active steroid. 4 mg of betamethasone disodium phosphate is the equivalent of 3 mg of betamethasone.

Betamethasone acetate, almost insoluble in water, is suspended in the preparation Celestone Chronodose. This corticosteroid ester is slowly hydrolyzed at the injection site.

After oral and parenteral administration, the plasma half-life of betamethasone is >5 hours. The biological half-life is between 36 and 54 hours. After IM injection, the peak plasma concentration of betamethasone disodium phosphate is recorded after 60 minutes, and the corticosteroid is excreted almost completely on the first day. Pharmacological activity persists after the disappearance of measurable plasma levels.

Betamethasone is metabolized in the liver. Betamethasone binds primarily to albumin. In patients with a liver disorder, its clearance is slower or delayed.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, benzalkonium chloride, disodium edetate, 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

The expiry date is indicated on the printing materials.

6.4 Special precautions for storage

Store at a temperature below 25°C.
Do not freeze.
Shake before use.

6.5 Nature and contents of container

Packages of 1 ampoule of 1 ml.

6.6 Special precautions for disposal and other handling

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

7. LICENSE HOLDER AND ADDRESS

Organon Pharma Israel Ltd.,1 Atir Yeda, Kfar Saba

8. MARKETING AUTHORIZATION NUMBER

131-43-23009

9. MANUFACTURER

Organon LLC, NJ USA

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