

PRESCRIBING INFORMATION

CELESTONE[®] SOLUSPAN[®]

(Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable
Suspension, USP)

Injectable Glucocorticoid

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CELESTONE® SOLUSPAN®

(Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension, USP)

PHARMACOLOGICAL CLASSIFICATION

Injectable Glucocorticoid

PHARMACOLOGY

CELESTONE® SOLUSPAN® 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. 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.

INDICATIONS

I.M. injection in allergic, dermatologic, rheumatic, and other conditions responsive to systemic corticosteroids, including bursitis; injection directly into the affected tissues in bursitis and associated inflammatory disorders of tendons such as tenosynovitis, and inflammatory disorders of muscle such as fibrosis and myositis; intra-articular and periarticular injection in rheumatoid arthritis and osteoarthritis; intralesional injection in various dermatologic conditions; and local injection in certain inflammatory and cystic disorders of the foot.

CONTRAINDICATIONS

CELESTONE® SOLUSPAN® is contraindicated in patients:

- who are hypersensitive to any components of this product
- with herpes simplex of the eye
- with systemic fungal infections.

Regional corticosteroid therapy is contraindicated in areas that are locally infected, although infection elsewhere in the body is not a contraindication to the use of corticosteroid regionally.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

PRECAUTIONS

General

Strict aseptic technique is mandatory in the use of CELESTONE® SOLUSPAN® injection. CELESTONE® SOLUSPAN® is not intended for intravenous or subcutaneous use.

Following intra-articular injection, a portion of the administered dose of CELESTONE® SOLUSPAN® is absorbed systemically. In patients being treated concomitantly with peroral and parenteral corticosteroids, especially those receiving large doses, the systemic absorption of the drug should be considered in determining intra-articular dosage.

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

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

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

Corticosteroids should be used with caution in: nonspecific 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. Fat embolism has been reported as a possible complication of hypercorticism.

Advise patients to inform subsequent physicians of the prior use of corticosteroids.

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.

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 antimicrobial therapy should be instituted.

Since complications of glucocorticosteroid treatment are dependent on dose, size and duration of treatment, a risk/benefit decision must be made with each patient.

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

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardiovascular/Renal

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine and Metabolism

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.

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual dosage reduction. Such relative insufficiency may persist for months after discontinuation of therapy; therefore, if stress occurs during that period, corticotherapy should be reinstated. If the patient is receiving corticosteroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticosteroid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (ie, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (ie, postmenopausal women) before initiating corticosteroid therapy.

Hematologic

Use ASA cautiously in conjunction with corticosteroids in hypoprothrombinemia.

CELESTONE[®] SOLUSPAN[®] injection should be administered intramuscularly with caution to patients with idiopathic thrombocytopenic purpura.

Hepatic/Biliary/Pancreatic

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

Immune

While on corticosteroid therapy, patients should not be vaccinated against smallpox because of potential complications. Conversely, patients with vaccinia should not receive corticosteroid

therapy. Other immunization procedures should not be undertaken in patients receiving corticosteroids, especially high doses, because of possible hazards of neurological complications and lack of antibody response. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison disease.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice. This is of particular importance in children.

The use of corticosteroids 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 antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy, patients should receive chemoprophylaxis. If rifampin is used in a chemoprophylactic program, its enhancing effect on metabolic hepatic clearance of corticosteroids should be considered; adjustment in corticosteroid dosage may be required.

Corticosteroids may mask some signs of infection, and new infections may appear during use. There may be decreased resistance and inability to localize infection when corticosteroids are used. If corticosteroids have to be used in the presence of bacterial infections, institute appropriate vigorous anti-infective therapy.

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

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. There have been

cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, and Toxoplasma.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

Neurologic

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.

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.

Ophthalmologic

Prolonged corticosteroid use may produce posterior subcapsular cataracts (especially in children), glaucoma with possible damage to the optic nerves, and may enhance secondary ocular infections due to fungi or viruses. Ophthalmologic examination should be done periodically, especially in patients on long-term therapy (more than six weeks).

The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Psychiatric

Psychic derangement 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 or psychotic tendencies may be aggravated by corticosteroids.

Sensitivity/Resistance

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.

Special Populations

Fertility

Corticosteroids have been shown to impair fertility in animal studies. Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnant and Nursing Woman

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

When mothers were given betamethasone injections prenatally, the infants had transient suppression of fetal growth hormone and presumably of those pituitary hormones which regulate corticosteroid production by both the definitive and fetal zones of the fetal adrenal glands. However, the suppression of fetal hydrocortisone did not interfere with the pituitary-adrenocortical responses to stress after birth.

Women who have been on corticosteroids during pregnancy should be monitored during and after labor and delivery for any indication of adrenal insufficiency because of the stresses associated with childbirth.

Corticosteroids cross the placental barrier and appear in breast milk of nursing mothers. Because transplacental passage of corticosteroids occurs, newborn and young infants born of mothers who were dosed with corticosteroids throughout most or some portion of their pregnancy should be examined carefully for signs of adrenal insufficiency and the possible very rare occurrence of congenital cataracts.

Because of the potential for unwanted adverse effects from CELESTONE® SOLUSPAN® Injection in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Since use of corticosteroids prophylactically beyond the 32nd week of gestation is still controversial, the risk/benefit ratio should be considered for mother and fetus when using corticosteroids beyond this gestational period.

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

Pediatrics (< 18 years of age)

Growth and development in infants and children on prolonged corticosteroid therapy should be carefully observed.

Monitoring and Laboratory Test

Corticosteroids may suppress reactions to skin tests.

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 affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

Drug Interactions

Concurrent use of phenobarbital, phenytoin, rifampin or ephedrine may enhance the metabolism and clearance of corticosteroids, reducing their therapeutic effects.

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

Concurrent use of corticosteroids with potassium-depleting diuretics may enhance hypokalemia. Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. Corticosteroids may enhance the potassium depletion caused by amphotericin B. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.

Concurrent use of corticosteroids with coumarin-type anticoagulants may increase or decrease the anticoagulant effects, possibly requiring adjustment in dosage.

Combined effects of non-steroidal anti-inflammatory drugs or alcohol with glucocorticosteroids may result in an increased occurrence or increased severity of gastrointestinal ulceration.

Corticosteroids may decrease blood salicylate concentrations. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Dosage adjustments of an antidiabetic drug may be necessary when corticosteroids are given to diabetics.

Concomitant glucocorticosteroid therapy may inhibit the response to somatotropin.

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

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

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Serum concentrations of isoniazid may be decreased.

Cholestyramine may increase the clearance of corticosteroids.

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

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

Corticosteroids may suppress reactions to skin tests.

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible.

ADVERSE EFFECTS

There have been a few cases of crystal deposition but no reports of dimpling of the skin after intradermal injection. Nevertheless, because dimpling of the skin is attributable to atrophy of subcutaneous fat and is seen with other injectable corticosteroids, subcutaneous injection should be avoided. Pain has not been reported.

Fluid and electrolyte disturbances: sodium retention, potassium loss, hypokalemic alkalosis; fluid retention; congestive heart failure in susceptible patients; hypertension.

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

Gastrointestinal: hiccups, peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis.

Dermatologic: impaired wound healing; skin atrophy; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; suppressed reactions to skin tests; reactions such as allergic dermatitis, urticaria, angioneurotic edema, hyperpigmentation, hypopigmentation, subcutaneous atrophy, cutaneous atrophy.

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 of insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: posterior subcapsular cataracts; increased intraocular pressure, glaucoma; exophthalmos, instances of blindness associated with intralesional therapy around the face and head.

Metabolic: negative nitrogen balance due to protein catabolism.

Psychiatric: euphoria, mood swings; severe depression to frank psychotic manifestations; personality changes; hyperirritability; insomnia.

Immune system disorders: hypersensitivity, anaphylactoid and hypotensive or shock like reactions.

Vascular disorders: thromboembolism

General disorders and administration site conditions: sterile abscess, post injection flare (following intraarticular use).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: Acute overdose with glucocorticosteroids, including betamethasone, is not expected to lead to a life-threatening situation. Except at the most extreme dosages, a few days of excessive glucocorticosteroid dosing is unlikely to produce harmful results in the absence of specific contraindications, such as in patients with diabetes mellitus, glaucoma, or active peptic ulcer, or in patients on medications such as digitalis, coumarin-type anticoagulants or potassium-depleting diuretics.

Treatment: Complications resulting from the metabolic effects of the 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. Treat electrolyte imbalance if necessary.

DOSAGE

Shake well before using. Dosage must be adjusted according to the severity of the condition, the response obtained, and the patient's tolerance to the corticosteroid. For system effect, treatment is initiated with 1 mL i.m. 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 dermatologic disorders, including neurodermatitis, psoriasis, hypertrophic lichen planus, lichen simplex, eczema, contact dermatitis, and dermatitis medicamentosa, i.m. dosage is usually 1 mL at intervals of 3 days to a week. In respiratory tract disorders, including bronchial asthma, hay fever, allergic bronchitis, and perennial allergic rhinitis, i.m. dosage is usually 1 to 2 mL at weekly intervals. Bursitis may be treated with i.m. injections of 1 mL repeated weekly if necessary.

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® SOLUSPAN® should be discontinued and other appropriate therapy initiated.

For local effect, in acute 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. Partial relief of pain and some increase in mobility may be expected in both conditions after 1 or 2 injections. In tendonitis, myositis, fibrositis, tenosynovitis, peritendonitis, and periarticular inflammatory conditions, 3 or 4 local injections of 1 ml each at intervals of 1 to 2 weeks between injections are given 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. Using sterile technique, a 20 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® SOLUSPAN® and the injection is then made into the joint (see Table 1).

Table I. CELESTONE® SOLUSPAN®**Intra-articular Injection**

Size of Joint	Location	Dose (mL)
Very Large	Hip	1.0 to 2.0
Large	Knee Ankle Shoulder	1.0
Medium	Elbow Wrist	0.5 to 1.0
Small (Metacarpophalangeal Intraphalangeal (Sternoclavicular)	Hand Chest	0.25 to 0.5

Pain with intra-articular injection of CELESTONE® SOLUSPAN® has not been a problem. However, should the physician want to administer it with a local anaesthetic, it can be mixed in the syringe with an equal volume of 1% or 2% lidocaine hydrochloride, procaine hydrochloride, or similar local anesthetics using formulations which do not contain parabens. Anesthetics containing methylparaben, propylparaben, phenol, etc. should be avoided. The required dose of CELESTONE® SOLUSPAN® is first withdrawn from the vial into the syringe. The local anesthetic is then drawn in, and the syringe is shaken briefly. Do not inject local anaesthetic into the vial of CELESTONE® SOLUSPAN®.

Dermatologic conditions that have responded to intralesional treatment with CELESTONE® SOLUSPAN® include: localized neurodermatitis, psoriasis, nummular eczema, alopecia areata, hypertrophic lichen planus, circumscribed lichen simplex, keloids, and chronic discoid lupus erythematosus. In intralesional treatment, 0.2 mL of CELESTONE® SOLUSPAN® is injected intradermally (not s.c.) per cm² of lesion using a tuberculin syringe with a 25 gauge, 13 mm needle. Care should be taken to deposit a uniform depot of medication intradermally. A total of no more than 1 mL at weekly intervals is recommended.

Disorders of the foot responsive to corticosteroids injected locally: For most injections into the foot, a tuberculin syringe with a 25 gauge, 2 cm needle is used. Treatment is given at intervals of 3 days to a week. In bursitis under heloma durum (hard corn), bursitis under heloma molle (soft corn), synovial cysts, and Morton's neuralgia (metatarsalgia) 0.25 to 0.5 mL are recommended. For bursitis under calcaneal spurs, bursitis under hallux rigidus (flexion deformity of the great toe), bursitis over digiti quinti varus (inward deviation of the fifth toe) tenosynovitis, and periosistitis of the cuboid, 0.5 mL is recommended; in acute gouty arthritis 0.5 to 1 mL are recommended.

SUPPLIED

Each **mL** of sterile aqueous suspension contains: **3 mg** betamethasone acetate and **3 mg** betamethasone (as betamethasone sodium phosphate). Nonmedicinal ingredients: benzalkonium chloride, disodium edetate, sodium phosphate dibasic, sodium phosphate monobasic and water. Vials of 1 mL. Boxes of 10 and multiple dose vials of 5 mL. Store between 2 and 30°C. Protect from light.