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Physician's Package Insert עלון לרופא

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DEXACORT® FORTE דקסאקורט® פורטה

SOLUTION FOR INJECTION להזרקה לתוך הוריד

Composition

Each ampoule of 1 ml contains:

Active Ingredient

Dexamethasone sodium phosphate 20 mg

Other Ingredients

Sodium citrate, creatinin, methylparaben, sodium metabisulfite, edetate disodium, propylparaben, sodium hydroxide normal 1N, water for injection.

Mechanism of Action

Dexamethasone is a synthetic glucocorticosteroid, used primarily for its potent anti-inflammatory effect. It has rapid onset but short duration of action, and is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Dexacort Forte is a formulation intended for i.v. use as adjunctive treatment of severe shock.

Indications

Intravenous use as adjunctive treatment of severe shock of hemorrhagic, traumatic, surgical or septic origin.

Contraindications

Known hypersensitivity to any ingredient of the product (including sulfites).

Systemic infection unless specific anti-infective therapy is employed

Systemic fungal infections (see also Warnings), bacteremia, unstable joints, infection at the injection site, e.g. septic arthritis resulting from gonorrhea or tuberculosis.

Systemic viral infections and patients with peptic ulcer, osteoporosis and psychoses

Immunization procedures with live, or live-attenuated vaccines, including smallpox, in patients receiving immunosuppressive doses of corticosteroids, because of possible neurological complications and a lack of antibody response.

Warnings

The lowest possible dose of corticosteroid should be used to control the condition being treated. When reduction in dosage is possible, it should be gradual.

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternative days. Frequent patient review is required to appropriately titrate the dose against disease activity.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis .

In patients receiving corticosteroid therapy and subjected to unusual stress, such as trauma or surgery, increased dosage of corticosteroids before, during and after the stressful situation, is indicated.

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. Anaphylactoid and hypersensitivity reactions have been reported for dexamethasone sodium phosphate Injection (see Adverse Reactions).

After parenteral administration of glucocorticoids serious anaphylactoid reactions, such as glottis oedema, urticaria and bronchospasm, have occasionally occurred, particularly in patients with a history of allergy. If such an anaphylactoid reaction occurs, the following measures are recommended: immediate slow intravenous injection of 0.1 - 0.5 ml of adrenaline (solution of 1:1000: 0.1 - 0.5 mg adrenaline dependent on body weight), intravenous administration of aminophylline and artificial respiration if necessary.

Corticosteroids should not be used for the management of head injury or stroke because it is unlikely to be of any benefit and may even be harmful

Dexacort Forte preparation contains a sulfite preservative which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown, but is probably low. Sulfite sensitivity is observed more frequently in asthmatic individuals.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium.
Dietary salt restriction and potassium supplementation may be necessary. Calcium levels should be monitored, since corticosteroids increase calcium excretion.

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

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results (see Diagnostic Interference). If an infection occurs during therapy, it should be promptly controlled by a suitable antimicrobial agent.

The use of systemic corticosteroids in active tuberculosis should be restricted to cases of fulminating or disseminated disease, where the corticosteroid is used for management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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 due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone, was followed by cardiac enlargement and congestive failure.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (Consult the respective prescribing information for VZIG and IG). If chicken pox develops, treatment with antiviral agents may be considered.

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 may activate latent amebiasis. Therefore, it is recommended that amebiasis, whether latent or active, should be ruled out before therapy with a corticosteroid is instituted in patients prone to the disease, e.g. patients with unexplained diarrhea or patients who have spent time in endemic areas.

It has been reported that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastrointestinal bleeding.

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.

Use in Pregnancy

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

Use in Breastfeeding

Corticosteroids appear in breast milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacological doses of corticosteroids should be advised not to breastfeed.

Use in the Elderly

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

Adverse Reactions

Local adverse reactions include post-injection flare, and a painless destruction of the joint reminiscent of Charcots arthropathy especially with repeated intra-articular injection.

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment. Cases of ruptured tendon have been reported.

Local injection of glucocorticoid may produce systemic effects

Fluid and Electrolyte Disturbances

Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

Musculoskeletal

Muscle weakness, steroid myopathy, loss of muscle mass (muscular atrophy) , tendon rupture, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fractures of long bones, proximal myopathy .

Gastrointestinal

Peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the intestine particularly in patients with inflammatory bowel disease, pancreatitis, candidiasis , abdominal distension, ulcerative esophagitis.

Dermatological

Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, increased sweating.

Corticosteroids may suppress reactions to skin tests.

Burning or tingling, especially in the perineal area (after I.V.injection).

Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema.

Neurological

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown

Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, psychic disturbances, euphoric side effects cerebral palsy in preterm infants.

Endocrine

Menstrual irregularities, amenorrhea, 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, hirsutism.

Opthalmological

Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmus, retinopathy of prematurity.

Metabolic

Negative nitrogen balance due to protein catabolism.

Blood/Vascular Disorders :

Thromboembolism, polymorphonuclear leucocytosis, neuropathy, vasculitis, development of Diabetes Mellitus

Effect on Bones and Joints

Osteoporosis, arthropathy, osteonecrosis of femoral and/or humeral heads (aseptic or avascular necrosis).

Cardiovascular

Myocardial rupture following recent myocardial infarction.
Hypertrophic cardiomyopathy in low birth weight infants
Impaired cardiac contractility

Anti-inflammatory and Immunosuppressive effects

Increased susceptibility and severity of infections with suppression of clinical symptoms and signs. Diminished lymphoid tissue and immune response. Opportunistic infections, recurrence of dormant tuberculosis and decreased responsiveness to vaccination and skin tests.

Other

Anaphylactoid or hypersensitivity reactions, thromboembolism, weight gain, increased appetite, nausea, malaise, hiccups.

The following additional adverse reactions are related to parenteral corticosteroid therapy: rare instances of blindness associated with intra-lesional 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.

Withdrawal Symptoms

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death.
A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Precautions

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case, as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by the gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy. Therefore, in any situation of stress occurring during this period, hormone therapy should be reinstituted. If the patient is receiving steroids already, the dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids have an enhanced effect on patients with hypothyroidism and hepatic cirrhosis.

Corticosteroids should be used with caution in patients with ocular herpes simplex because of possible corneal perforation.

Psychic derangements may appear when corticosteroids are used. These can range from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. In addition, corticosteroids may aggravate existing emotional instability or psychotic tendencies.

Co-administration of thalidomide with dexamethasone phosphate injection should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

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

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. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Growth and development of infants and children receiving prolonged corticosteroid therapy should be carefully observed.

Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray, should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

Special Precautions

(see also Contraindications)

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

a. Osteoporosis (post-menopausal females are particularly at risk).
b. Hypertension or congestive heart failure.
c. Existing or previous history of severe affective disorders (especially previous steroid psychosis).
d. Diabetes mellitus (or a family history of diabetes).
e. History of tuberculosis, since glucocorticoids may induce reactivation.
f. Glaucoma (or a family history of glaucoma).
g. Previous corticosteroid-induced myopathy.
h. Liver failure.
i. Renal insufficiency.
j. Epilepsy.
k. Gastro-intestinal ulceration.

l. Migraine
m. Certain parasitic infestations in particular amoebiasis.
n. Incomplete statural growth since glucocorticoids on prolonged administration may accelerate epiphyseal closure
o. Patients with Cushing's syndrome
In the treatment of conditions such as tendinitis or tenosynovitis care should be taken to inject into the space between the tendon sheath and the tendon as cases of ruptured tendon have been reported.

Drug Interactions
Dexamthasone/Erythromycin/Indinavir Dexamethasone is a moderate inducer of CYP 3A4.Co-administration of dexamethasone with other drugs that are metabolized by CYP 3A4 (e.g.,indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.
CorticosteroidsCytochrome P450 3A4 {CYP 3 A4} Enzyme Inducers (such as Phenytoin, Primidone, Phenylbutazone Carbamazepine, Phenobarbital, Rifampicin, Rifabutin, Aminoglutethemide) : Cytochrome P450 3A4 (CYP 3A4) enzyme inducers, such as phenytoin, barbiturates (e.g., phenobarbital), carbamazepine, and rifampin may enhance the metabolic clearance of corticosteroids. resulting in reduced therapeutic effects, that require dosage adjustment of the corticosteroid to achieve the desired response.
Corticosteroids/Ephedrine: Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage
Corticosteroids/CYP Inhibitors such as Troleandomycin, Ketoconazole Isoniazid, Estrogen or Estrogen-Containing Contraceptives*:* Concurrent administration may lead to a significant decrease in the clearance of the corticosteroid, through inhibition of its metabolism. Therefore, the dose of the corticosteroid should be titrated to avoid steroid toxicity.
Corticosteroids/Cyclosporine*:* Concurrent use leads to mutual inhibition of metabolism. It is possible that adverse events associated with individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use. Although the combination is therapeutically beneficial for organ transplants, toxicity may be increased, and should be taken into consideration.
Corticosteroids/Digitalis Glycosides*:* Concurrent use may increase the possibility of digitalis toxicity associated with hypokalemia.
Corticosteroids/Potassium-depleting Diuretics/Amphotericin B/Carbonic Anhydrase Inhibitors*:* Concurrent use may cause hypokalemia; serum potassium level should be determined at frequent intervals.
Corticosteroids/Hypoglycemics/Streptozocin/Asparaginase: Corticosteroids may increase blood glucose levels; dosage adjustment of the antidiabetic agent is necessary.
Corticosteroids/Anticoagulants*:* Corticosteroids may alter the response to coumarin anticoagulants. Therefore, caution is recommended when these drugs are used concurrently, especially in patients prone to gastrointestinal ulceration and hemorrhage. Therefore, coagulation indices should be frequently monitored during and after glucocorticoid therapy to maintain the desired anticoagulant effect.
Corticosteroids/Aspirin*:* Corticosteroids may increase the clearance of chronic high-dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when the steroid is withdrawn. Special caution is required in patients presenting with hypoprothrombinemia.
Corticosteroids/Anticholinesterases*:* Concurrent administration may antagonise the anticholinesterase effects in myasthenia gravis.

Corticosteroids/Potassium Supplements/Potassium-Sparing Diuretics*:* Concomitant use of these medications may cause a decrease in serum potassium concentration; monitoring of serum potassium concentration is recommended.
Corticosteroids/Ritodrine*:* Concurrent use may cause pulmonary edema in the mother. Maternal death has been reported. Therefore, both medications should be discontinued at the first sign of pulmonary edema.
Corticosteroids/ Mexiletine*:* Concurrent use may accelerate mexiletine metabolism, leading to decreased mexiletine plasma concentration.
Corticosteroids/Somatropin*:* Concomitant administration may lead to inhibition of the growth response to somatropin. this may occur with daily doses of oral or parenteral corticosteroid (calculated per square meter of body surface) in excess of:
375-563 micrograms/ml for oral dexamethasone
187.5-281.5 micrograms/ml for parenteral dexamethasone
10-15 mg for oral hydrocortisone
5-7.5 mg for parenteral hydrocortisone.
Therefore, it is recommended that these doses of the corticosteroids should not be exceeded during somatropin therapy. If larger doses of the corticosteroids are required, the administration of somatropin should be postponed.
Concurrent use of somatropin with corticotropin is not recommended.
Corticosteroids/ Vaccines, Live Virus or Other Immunizations*:* Immunizations are not recommended in receiving pharmacologic (immunosuppressant) doses of glucocorticoisteroids because of the increased risk of neurological complications and the possibility of decreased or absent antibody response (see also contraindications, Warnings).

Diagnostic Interference

Blood and urine glucose, and serum cholesterol levels may be increased.

Decreased serum levels of potassium, triiodothyronine (T_3), and a minimal decrease of thyroxine (T_4) may occur. Thyroid I^{131} uptake may be decreased.

Corticosteroids may effect the nitroblue-tetrazolium test for bacterial infection and produce false-negative results.

False negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Therefore, DST results should be interpreted with caution in these patients.

Basophil, eosinophil, lymphocyte and monocyte counts may be decreased.

Serum calcium concentrations may be decreased.

In skin tests, including tuberculin and histoplasmin skin tests and patch tests for allergy, reactions may be suppressed, especially with daily administration of large doses of corticosteroids.

Information for Patients

General

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure, although dose levels do not allow prediction of the onset, type severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

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

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise is suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided.

Corticosteroids should not be injected into unstable joints.

Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

Frequent intra-articular injection may result in damage to joint tissues.

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

Susceptible patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Pediatric Use: Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully followed.

Dosage and Administration

Notes

Corticosteroid therapy is an adjunct to, and not replacement for, conventional therapy. Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Dosage requirements are variable, and must be individualized on the basis of the disease and the response of the patient.

Dexacort Forte Injection, which is indicated for the adjunctive treatment of severe shock, must be given by i.v. administration only.

Reported regimens range from 1-6 mg/kg body weight as a single i.v. injection, to 40 mg initially followed by repeated i.v. injections every 2-6 hours, while shock persists.

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized, and usually not longer than 48-72 hours. Although adverse reactions associated with high dose, short-term corticosteroid therapy are uncommon, peptic ulceration may occur.

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

Significant lethality was observed in female mice at single oral doses of 3630mg/m^2 (1210 mg/kg) and single intravenous doses of 2382 mg/m^2 (794 mg/kg).

Storage

Store below 25°C.
Store in the original container in order to protect from light.

Drug Registration No: 127 46 21680 21

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