

PHYSICIANS CIRCULAR

DECADRON[®] Phosphate (dexamethasone sodium phosphate, USP)

Injection DECADRON[®] Phosphate (dexamethasone sodium phosphate, USP) is a synthetic glucocorticoid used primarily for its anti-inflammatory effects. It is among the most potent glucocorticoids, having about 25 to 30 times the anti-inflammatory activity of hydrocortisone. In contrast, its effect on electrolytes is slight. At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

In addition to its anti-inflammatory properties, Injection DECADRON Phosphate has been shown to be effective in the management of nausea and vomiting secondary to cisplatin and non-cisplatin emetogenic chemotherapy.

Glucocorticoids cause profound and varied metabolic effects. They also modify the body's immune response to diverse stimuli.

Injection DECADRON Phosphate is a versatile corticosteroid which, because it is presented as a solution, may be administered intravenously, intramuscularly, intra-articularly, or intrabursally.

INDICATIONS

Conditions where the anti-inflammatory and immunosuppressive effects of the corticosteroids are desirable, especially for intensive treatment during shorter periods. (For a listing of specific indications see SUPPLEMENTAL PRESCRIBING INFORMATION, SPECIFIC INDICATIONS.)

In addition, for the management of nausea and vomiting associated with cisplatin and non-cisplatin emetogenic chemotherapy.

DOSAGE AND ADMINISTRATION

Each milliliter contains dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate (equal to 3.33 mg of dexamethasone or roughly about 100 mg of hydrocortisone). Inactive ingredients per mL: 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, and Water for Injection, q.s. 1 mL, with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when sterilization of the exterior of the vial is desired. Protect from freezing.

This preparation can be given directly from the vial without mixing or dilution. If preferred, it can be added to Sodium Chloride Injection, or Dextrose Injection, without loss of potency, and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative free when used in the neonate, especially the premature infant.

When DECADRON Phosphate injection is added to an infusion solution, the mixture must be used within 24 hours since infusion solutions do not contain preservatives.

The usual aseptic techniques governing injections should be observed.

INTRAVENOUS AND INTRAMUSCULAR INJECTION

The usual initial dosage of DECADRON Phosphate injection may vary from 0.5 mg to 20 mg per day depending on the specific disease entity being treated. Usually the parenteral dose is one-third to one-half the oral dose, given every 12 hours. However, in certain overwhelming, acute, life-threatening situations, dosages exceeding the usual recommended dosages have been used. In these circumstances, the slower rate of absorption by intramuscular administration should be recognized.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. If the drug is to be stopped after it has been given for more than a few days, it is recommended that it be withdrawn gradually rather than stopped abruptly.

In emergencies, the usual dose is 1 mL to 5 mL (4 mg to 20 mg) I.V. or I.M. (in shock use only the I.V. route). This dose may be repeated until adequate response is noted.

After initial improvement, single doses of 0.5 mL to 1 mL (2 mg to 4 mg) should be repeated as necessary. The total daily dosage usually need not exceed 20 mL (80 mg), even in severe conditions.

When constant maximal effect is desired, dosage must be repeated at three-hour or four-hour intervals, or maintained by slow intravenous drip.

Intravenous and intramuscular injections are advised in acute illness. When the acute stage has passed, substitute oral steroid therapy as soon as feasible.

ANTIEMETIC PROPHYLAXIS DURING EMETOGENIC CHEMOTHERAPY

In clinical studies, 8 - 20 mg of dexamethasone was infused intravenously over 5 - 15 minutes just prior to chemotherapy, followed by 4 mg of dexamethasone orally every 4 - 6 hours, or by 8 mg orally every 8 hours, and tapered in either strength or frequency of administration over two to three days. In general, the total treatment duration for this indication should not exceed five days beyond chemotherapy. Alternatively, injectable dexamethasone was infused intravenously in lieu of an oral formulation of dexamethasone, using various schedules. (See CLINICAL STUDIES for additional information on dosage and administration.)

Use With Other Antiemetic Agents: Some patients have received dexamethasone concomitantly with ondansetron to achieve enhanced efficacy for antiemetic prophylaxis during cisplatin or non-cisplatin emetogenic chemotherapy. The dosage of dexamethasone employed in combination therapy was similar to its dosage when administered alone. (See CLINICAL STUDIES for additional information on dosage and administration.)

Concomitant administration of dexamethasone and metoclopramide has also demonstrated enhanced efficacy for antiemetic prophylaxis during emetogenic chemotherapy.

SHOCK (OF HEMORRHAGIC, TRAUMATIC, OR SURGICAL ORIGIN)

The usual dose is 2 to 6 mg/kg body weight given as a single intravenous injection. This may be repeated in 2 to 6 hours, if shock persists. As an alternative, Injection DECADRON Phosphate, 2 to 6 mg/kg body weight, is given as a single intravenous injection followed immediately by the same dose in an intravenous infusion. Therapy with Injection DECADRON Phosphate is an adjunct to, and not a replacement for, conventional therapy (see PRECAUTIONS).

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually no longer than 48 to 72 hours.

CEREBRAL EDEMA

Associated with primary or metastatic brain tumor, neurosurgery, head injury, pseudotumor cerebri or preoperative preparation of patients with increased intracranial pressure secondary to brain tumor: Initially 10 mg (2.5 mL) DECADRON Phosphate injection intravenously followed by 4 mg (1 mL) intramuscularly every 6 hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours: dosage may be reduced after 2 to 4 days and gradually discontinued over a period of 5 to 7 days.

High doses of Injection DECADRON Phosphate are recommended for initiating short-term intensive therapy for acute life-threatening cerebral edema. Following the high loading dose schedule of the first day of therapy, the dose is scaled down over the 7 to 10 day period of intensive therapy and subsequently reduced to zero over the next 7 to 10 days. When maintenance therapy is required, this should be changed to oral DECADRON as soon as possible.

Suggested high dose schedule in cerebral edema. (See chart below).

Suggested High Dose Schedule in Cerebral Edema

Adults

| | |
|----------------|-------------------------------------|
| Initial Dose | 50 mg, I.V. |
| 1st day | 8 mg, I.V. every 2 hours |
| 2nd day | 8 mg, I.V. every 2 hours |
| 3rd day | 8 mg, I.V. every 2 hours |
| 4th day | 4 mg, I.V. every 2 hours |
| 5th to 8th day | 4 mg, I.V. every 4 hours |
| Thereafter | decrease by daily reduction of 4 mg |

Children (35 kg and over)

| | |
|----------------|-------------------------------------|
| Initial Dose | 25 mg, I.V. |
| 1st day | 4 mg, I.V. every 2 hours |
| 2nd day | 4 mg, I.V. every 2 hours |
| 3rd day | 4 mg, I.V. every 2 hours |
| 4th day | 4 mg, I.V. every 4 hours |
| 5th to 8th day | 4 mg, I.V. every 6 hours |
| Thereafter | decrease by daily reduction of 2 mg |

Children (below 35 kg)

| | |
|----------------|-------------------------------------|
| Initial Dose | 20 mg, I.V. |
| 1st day | 4 mg, I.V. every 3 hours |
| 2nd day | 4 mg, I.V. every 3 hours |
| 3rd day | 4 mg, I.V. every 3 hours |
| 4th day | 4 mg, I.V. every 6 hours |
| 5th to 8th day | 2 mg, I.V. every 6 hours |
| Thereafter | decrease by daily reduction of 1 mg |

Note: For this high dose regimen, the use of the high strength product form, Injection DECADRON 20 (20 mg/mL) may be more convenient.*

* Should be omitted by those countries not marketing Injection DECADRON 20.

For palliative management of patients with recurrent or inoperable brain tumors: Maintenance therapy should be individualized with DECADRON Phosphate injection, DECADRON Tablets or DECADRON Elixir. A dosage of 2 mg 2 or 3 times a day may be effective.

Associated with acute stroke (excluding intracerebral hemorrhage): Initially 10 mg (2.5 mL) DECADRON Phosphate injection intravenously followed by 4 mg (1 mL) intramuscularly every 6 hours for 10 days.

Doses should then be tapered to zero over the ensuing 7 days.

The smallest dosage necessary to control cerebral edema should be utilized.

DUAL THERAPY

In acute self-limited allergic disorders or acute exacerbations of chronic allergic disorders, (e.g., acute allergic rhinitis, acute attacks of seasonal allergic bronchial asthma, urticaria medicamentosa, and contact dermatoses), the following dosage schedule combining parenteral and oral therapy is suggested:

| | | Total Daily Dosage |
|---------|---|--------------------|
| 1st day | one or two mL (4 to 8 mg) of Injection DECADRON Phosphate intramuscularly | 4 or 8 mg |
| 2nd day | two 0.5 mg Tablets DECADRON b.i.d. | 4 tablets |
| 3rd day | two 0.5 mg Tablets DECADRON b.i.d. | 4 tablets |
| 4th day | one 0.5 mg Tablet DECADRON b.i.d. | 2 tablets |
| 5th day | one 0.5 mg Tablet DECADRON b.i.d. | 2 tablets |
| 6th day | one 0.5 mg Tablet DECADRON per day | 1 tablet |
| 7th day | one 0.5 mg Tablet DECADRON per day | 1 tablet |
| 8th day | follow-up visit | |

INTRA-ARTICULAR, INTRALESIONAL, AND SOFT-TISSUE INJECTION

Intra-articular, intralesional, and soft-tissue injections generally are employed when affected joints or areas are limited to one or two sites.

Some of the usual single doses are:

| Site of Injection | Volume of Injection (mL) | Amount of Dexamethasone Phosphate (mg) |
|---|--------------------------|--|
| Large Joints (e.g., Knee) | 0.5 to 1 | 2 to 4 |
| Small Joints (e.g., Interphalangeal, Temporomandibular) | 0.2 to 0.25 | 0.8 to 1 |
| Bursae | 0.5 to 0.75 | 2 to 3 |
| Tendon Sheaths | 0.1 to 0.25 | 0.4 to 1 |
| Soft-tissue Infiltration | 0.5 to 1.5 | 2 to 6 |
| Ganglia | 0.25 to 0.5 | 1 to 2 |

The frequency of injection varies from once every 3 to 5 days to once every 2 to 3 weeks, depending on the response to treatment.

NEONATAL RESPIRATORY DISTRESS SYNDROME: Antenatal Prophylaxis

The recommended dosage of DECADRON Phosphate injection is 5 mg (1.25 mL) administered intramuscularly to the mother every twelve hours for up to a total of four doses. Administration should be initiated preferably between 24 hours and seven days before estimated delivery.

CONTRAINDICATIONS

Systemic fungal infections (See PRECAUTIONS regarding amphotericin B).

Hypersensitivity to sulfites or any other component of this medication (see PRECAUTIONS).

Administration of live virus vaccines (see PRECAUTIONS).

PRECAUTIONS

Injection DECADRON Phosphate contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening 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.

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.

Average and large doses of cortisone or hydrocortisone 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 necessary. All corticosteroids increase calcium excretion.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by 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 that period, corticosteroid therapy should be reinstated or the current dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. (See DRUG INTERACTIONS.)

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.

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.

Administration of live virus vaccines 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.

The use of DECADRON Phosphate injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the 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.

Steroids 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. 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.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis. Steroids may increase or decrease motility and number of spermatozoa in some patients.

Corticosteroids may mask some signs of infection, and new infections may appear during their use.

In cerebral malaria, the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis or strongyloidiasis or exacerbate active disease. Therefore, it is recommended that latent or active amebiasis and strongyloidiasis be ruled out before initiating corticosteroid therapy in any patient at risk of or with symptoms suggestive of either condition.

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

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

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

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

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

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

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

Corticosteroids should not be injected into unstable joints.

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

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.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox 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. The risk of developing a disseminated infection varies among individuals and may be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. Exposed patients should be advised to seek medical advice without delay. If exposed to measles, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. (See the respective package inserts for IG and VZIG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

USE IN PREGNANCY AND NURSING MOTHERS

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

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects in the breastfeeding infant. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

DRUG INTERACTIONS

Co-administration of thalidomide with Injection DECADRON Phosphate should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Cytochrome P450 3A4 (CYP 3A4) enzyme inducers, such as phenytoin (diphenylhydantoin), barbiturates (e.g., phenobarbital), carbamazepine, and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage.

Dexamethasone is metabolized by CYP 3A4. Concomitant administration of dexamethasone with inducers of CYP 3A4 (as listed above) has the potential to result in decreased plasma concentrations of dexamethasone. In addition, concomitant administration of dexamethasone with known inhibitors of CYP 3A4 (e.g., ketoconazole, macrolide antibiotics such as erythromycin) has the potential to result in increased plasma concentrations of dexamethasone. Effects of other drugs on the metabolism of dexamethasone may interfere with dexamethasone suppression tests, which should be interpreted with caution during administration of such drugs.

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.

In post-marketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone co-administration, leading to alterations in seizure control.

Although ketoconazole may increase dexamethasone plasma concentrations through inhibition of CYP 3A4, ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal (see PRECAUTIONS).

Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage.

False-negative results in the dexamethasone suppression test in patients being treated with indomethacin have been reported.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

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

SIDE 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
- Osteoporosis
- Vertebral compression fractures
- Aseptic necrosis of femoral and humeral heads
- Pathologic fracture of long bones
- Tendon rupture

GASTROINTESTINAL

- Peptic ulcer with possible perforation and hemorrhage
- Perforation of the small and large bowel, particularly in patients with inflammatory bowel disease
- Pancreatitis
- Abdominal distention
- Ulcerative esophagitis

DERMATOLOGIC

- Impaired wound healing
- Thin fragile skin
- Petechiae and ecchymoses
- Erythema
- Increased sweating
- 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

Convulsions
Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment
Vertigo
Headache
Psychic disturbances
Cerebral palsy in preterm infants

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
Hyperglycemia
Increased requirements for insulin or oral hypoglycemic agents in diabetes
Hirsutism

OPHTHALMIC

Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma
Exophthalmos
Retinopathy of prematurity

METABOLIC

Negative nitrogen balance due to protein catabolism

CARDIOVASCULAR

Myocardial rupture following recent myocardial infarction (see PRECAUTIONS)
Hypertrophic cardiomyopathy in low birth weight infants

OTHER

Anaphylactoid or hypersensitivity reactions
Thromboembolism
Weight gain
Increased appetite
Nausea
Malaise
Hiccups

The following additional side effects are related to parenteral corticosteroid therapy:
Rare instances of blindness associated with intralesional therapy around the face and head
Hyperpigmentation or hypopigmentation
Subcutaneous and cutaneous atrophy
Sterile abscess
Postinjection flare (following intra-articular use)
Charcot-like arthropathy

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. There are no specific recommendations for the treatment of overdosage with Injection DECADRON Phosphate.

HOW SUPPLIED

Decadron[®] Injection is supplied in 1ml (25 X 1ml pack) and 5 ml vials. Each ml contains Dexamethasone Sodium Phosphate U.S.P equivalent to 4mg Dexamethasone.