

SUMMARY PRODUCT CHARACTERISTIC (SPC)

DEXAMETHASONE 4 MG / ML SOLUTION FOR INJECTION

1.1 TRADE NAME – Dexamethasone

1.2 INTERNATIONAL NON-PROPERTY NAME – Dexamethasone

2. COMPOSITION

Each 1 ml Dexamethasone, solution for injection, contains 4.37 mg of Dexamethasone sodium phosphate (equivalent to 4 mg dexamethasone phosphate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid

For use in certain endocrine and non-endocrine disorders responsive to corticosteroid therapy

Systemic (intravenous or intramuscular) administration

Dexamethasone solution for injection is recommended for systemic administration by intravenous or intramuscular injection when oral therapy is not feasible or desirable in the following conditions:

Endocrine disorders

Primary or secondary adrenocortical insufficiency

(Hydrocortisone or cortisone is the first choice, but synthetic analogues may be used with mineralocorticoids where applicable and, in infancy, mineralocorticoid supplementation is particularly important)

Non-endocrine disorders

Dexamethasone solution for injection may be used in the treatment of non-endocrine corticosteroid-responsive conditions, including:

Allergy and anaphylaxis

Angioneurotic oedema and anaphylaxis

Gastrointestinal disorders

Crohn's disease and ulcerative colitis

Infection (with appropriate chemotherapy)

Miliary tuberculosis and endotoxic shock

Neurological disorders

Raised intracranial pressure secondary to cerebral tumours and infantile spasms. In addition, dexamethasone for injection is used as an adjunct in the control of cerebral oedema caused by brain tumours or associated with neurosurgery, but not in those cases where the oedema is caused by head injury.

Respiratory disorders

Bronchial asthma and aspiration pneumonitis.

Skin disorders

Toxic epidermal necrolysis

Shock

Adjunctive treatment where high pharmacological doses are needed. Treatment is an adjunct to and not a substitute for, specific and supportive measures the patient may require. Dexamethasone has been shown to be beneficial when used in the early treatment of shock, but it may not influence overall survival.

Local administration

Dexamethasone solution for injection is suitable for intra-articular or soft-tissue injection as adjunctive therapy for short-term administration in:

Soft-tissue disorders

Such as carpal tunnel syndrome and tenosynovitis

Intra-articular disorders

Such as rheumatoid arthritis and osteoarthritis with an inflammatory component

Dexamethasone solution for injection may be injected intralesionally in selected skin disorders such as cystic acne vulgaris, localised lichen simplex, and keloids.

4.2 Posology and method of administration

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

In neonates, especially the premature infant, only preservative-free solutions should be administered.

Posology

Intravenous and Intramuscular Injection

Usually the parenteral dose is one-third to one half the oral dose, given every 12 hours. The usual initial dosage of dexamethasone solution for injection is 0.48 mg – 20 mg (0.12 ml – 5.0 ml) and varies depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice. 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.

Both the dose in the evening, which is useful in alleviating morning stiffness and the divided dosage regimen are associated with greater suppression of the hypothalamo-pituitary-adrenal axis. After a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial dosage by small amounts at appropriate intervals to the lowest dosage which will maintain an adequate clinical response. Chronic dosage should preferably not exceed 500 micrograms dexamethasone daily. Close monitoring of the drug dosage is needed.

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.

Whenever possible, the intravenous route should be used for the initial dose and for as many subsequent doses as are given while the patient is in shock (because of the irregular rate of absorption of any medicament administered by any other route in such patients). When the blood pressure responds, use the intramuscular route until oral therapy can be substituted. For the comfort of the patient, not more than 2 ml should be injected intramuscularly at any one site.

In emergencies, the usual dose is 4.0 mg to 20.0 mg (1.0 ml to 5.0 ml) 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 2.0 mg to 4.0 mg (0.5 ml to 1.0 ml) should be repeated as necessary. The total daily dosage usually need not exceed 80.5 mg (20.1 ml), 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.

Adults and Elderly

Once the disease is under control the dosage should be reduced or tapered off to the lowest suitable level under continuous monitoring and observation of the patient (see section 4.4).

For acute life-threatening situations (e.g. anaphylaxis, acute severe asthma) substantially higher dosages may be needed.

Cerebral oedema (adults): initial dose 8-16 mg IV followed by 5 mg IV or IM every 6 hours, until a satisfactory result has been obtained. In brain surgery these dosage may be

necessary until several days after the operation. Thereafter, the dosage has to be tapered off gradually. Increase of intracranial pressure associated with brain tumors can be counteracted by continuous treatment

Shock (Of Haemorrhagic, Traumatic, or Surgical Origin)

The usual dose is 2 to 6 mg/kg (0.5 ml – 1.5 ml/kg) body weight given as a single intravenous injection. This may be repeated in 2 to 6 hours, if shock persists. As an alternative, this may be followed immediately by the same dose in an intravenous infusion. Therapy with dexamethasone solution for injection is an adjunct to, and not a replacement for, conventional therapy.

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 Oedema

Associated with primary or metastatic brain tumour, pseudo-tumour cerebri or preoperative preparation of patients with increased intracranial pressure secondary to brain tumour:

Initially 10.0 mg (2.5 ml) dexamethasone solution for injection intravenously followed by 4 mg (1.0 ml) intramuscularly every 6 hours until symptoms of cerebral oedema 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 dexamethasone solution for injection are recommended for initiating short-term intensive therapy for acute life-threatening cerebral oedema. 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 dexamethasone as soon as possible.

Suggested high dose schedule in cerebral oedema is listed in the chart below:

<u>Adults</u>	
• Initial Dose	50 mg (12.5 ml), I.V.
• 1st day	8 mg (2.0 ml), I.V. every 2 hours
• 2nd day	8 mg (2 ml) mg, I.V. every 2 hours
• 3rd day	8 mg (2.0 ml) mg, I.V. every 2 hours
• 4th day	4 mg (1.0 ml), I.V. every 2 hours
• 5th to 8th day	4 mg (1.0 ml), I.V. every 4 hours
• Thereafter	decrease by daily reduction of 4 mg (1.0 ml)
<u>Children (35 kg and over)</u>	
• Initial Dose	25 mg (6.25 ml), I.V.
• 1st day	4 mg (1.0 ml), I.V. every 2 hours
• 2nd day	4 mg (1.0 ml), I.V. every 2 hours
• 3rd day	4 mg (1.0 ml), I.V. every 2 hours
• 4th day	4 mg (1.0 ml), I.V. every 4 hours
• 5th to 8th day	4 mg (1.0 ml), I.V. every 6 hours
Thereafter	decrease by daily reduction of 2 mg (0.5 ml)
<u>Children (below 35 kg)</u>	
• Initial Dose	20 mg (5.0 ml), I.V.
• 1st day	4 mg (1.0 ml), I.V. every 3 hours
• 2nd day	4 mg (1.0 ml), I.V. every 3 hours
• 3rd day	4 mg (1.0 ml), I.V. every 3 hours
• 4th day	4 mg (1.0 ml), I.V. every 6 hours
• 5th to 8th day	2 mg (0.5 ml), I.V. every 6 hours
• Thereafter	decrease by daily reduction of 1 mg (0.25 ml)

For palliative management of patients with recurrent or inoperable brain tumours.

Maintenance therapy should be individualized with dexamethasone solution for injection or dexamethasone tablets. A dosage of 2 mg (0.5 ml) 2 or 3 times a day may be effective.

Dual Therapy

In acute self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:

		Total Daily Dosage
1st day	1.0 ml to 2.0 ml of dexamethasone injection intramuscularly	4 to 8 mg
2nd day	two 0.5 mg dexamethasone tablets b.i.d.	4 tablets
3rd day	two 0.5 mg dexamethasone tablets b.i.d.	4 tablets
4th day	one 0.5 mg dexamethasone tablet b.i.d.	2 tablets
5th day	one 0.5 mg dexamethasone tablet b.i.d.	2 tablets
6th day	one 0.5 mg dexamethasone tablet.	1 tablets
7th day	one 0.5 mg dexamethasone tablet.	1 tablets
8th day	follow-up visit/reassessment day	

Intra-Articular, Intralesional, and Intra-Bursal Injection

Intra-articular, intralesional, and intra-bursal 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 (mg)
Large Joints (e.g., Knee)	0.5 to 1.0	2 – 4
Small Joints (e.g., Interphalangeal, Temporomandibular)	0.2 to 0.25	0.8 – 1.0
Bursae	0.5 to 0.75	2.0 – 3.0
Tendon Sheaths*	0.1 to 0.25	0.4 – 1.0
Soft-tissue Infiltration	0.5 to 1.5	2.0 – 6.0
Ganglia	0.24 to 0.5	0.97 – 2.0

*Injection should be made into the tendon sheath and not directly into the tendon.

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.

Special Populations

Paediatric population

Dosage requirements are variable and may have to be changed according to individual needs. Dosage should be limited to a single dose on alternate days to lessen retardation of growth and minimise suppression of the hypothalamo-pituitary adrenal axis.

Use in the elderly

Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life threatening reactions.

Method of administration

Dexamethasone solution for injection may be administered intravenously, intramuscularly, or by local injection (intra-articular or soft tissue). For administration by intravenous infusion: see section on compatibility with infusion fluids. With intravenous administration high plasma levels can be obtained rapidly.

Rapid intravenous injection of massive doses of glucocorticoids may sometimes cause cardiovascular collapse; the injection should therefore be given slowly over a period of several minutes.

Intra-articular injections should be given under strictly aseptic conditions.

4.3 Contraindications

Systemic infection unless specific anti-infective therapy is employed.

Hypersensitivity to any ingredient.

Local injection of a glucocorticoid is contraindicated in bacteraemia and systemic fungal infections, unstable joints, infection at the injection site e.g. septic arthritis resulting from gonorrhoea or tuberculosis.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

Severe allergic reactions. 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.

Tumor lysis syndrome. In post-marketing experience tumour lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 for pharmacokinetic interactions that can increase the risk of side effects), 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.

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.

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.

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, treat the patient with adrenaline and positive pressure ventilation.

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.

The results of a randomised, placebo-controlled study suggest an increase in mortality if methylprednisolone therapy starts more than two weeks after the onset of Acute Respiratory Distress Syndrome (ARDS). Therefore, treatment of ARDS with corticosteroids should be initiated within the first two weeks of onset of ARDS. (See also section 4.2).

Preterm neonates

Available evidence suggests long-term neurodevelopment adverse events after early treatment (<96 hours) of premature infants with chronic lung disease at starting doses of 0.25 mg/kg twice daily.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy was reported after systemic administration of corticosteroids including dexamethasone to prematurely born infants. In the majority of cases reported, this was reversible on withdrawal of treatment. In preterm infants treated with systemic dexamethasone diagnostic evaluation and monitoring of cardiac function and structure should be performed (section 4.8).

Dexamethasone withdrawal

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1 mg dexamethasone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 1 mg dexamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 6 mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 6 mg daily of dexamethasone.
- Patients repeatedly taking doses in the evening.

During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Patients should carry 'steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Serious Neurologic Adverse Reactions with Epidural 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.

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

Visual disturbance

Visual disturbance may be reported with systemic and topical 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 which may include posterior subcapsular cataracts glaucoma with possible damage to the optic nerves, secondary ocular infections due to fungi or viruses, or rare diseases such as central serous chorioretinopathy (CSCR).

Immunosuppression and Increased Risk of Infection

Corticosteroids, including Dexamethasone, suppress the immune system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic pathogens. Corticosteroids can:

- Reduce resistance to new infections,
- Exacerbate existing infections,
- Increase the risk of disseminated infections,
- Increase the risk of reactivation or exacerbation of latent infections,
- Mask some signs of infection.

Corticosteroid-associated infections can be mild but can be severe and at times fatal. The rate of infectious complications increases with increasing corticosteroid dosages. Monitor for the development of infection and consider Dexamethasone withdrawal or dosage reduction as needed.

Do not administer Dexamethasone by an intraarticular, intrabursal, intratendinous, or intralesional route in the presence of acute local infection.

Tuberculosis

If Dexamethasone is used to treat a condition in patients with latent tuberculosis or tuberculin reactivity, reactivation of the disease may occur. Closely monitor such patients for reactivation. During prolonged Dexamethasone therapy, patients with latent tuberculosis or tuberculin reactivity should receive chemoprophylaxis.

Varicella Zoster and Measles Viral Infections

Varicella and measles can have a serious or even fatal course in non-immune patients taking corticosteroids, including Dexamethasone. In corticosteroid-treated patients who have not had these diseases or are non-immune, particular care should be taken to avoid exposure to varicella and measles:

- If a Dexamethasone -treated patient is exposed to varicella, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If varicella develops, treatment with antiviral agents may be considered.
- If a Dexamethasone -treated patient is exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated.

Hepatitis B Virus Reactivation

Hepatitis B virus reactivation can occur in patients who are hepatitis B carriers treated with immunosuppressive dosages of corticosteroids, including Dexamethasone. Reactivation can also occur infrequently in corticosteroid-treated patients who appear to have resolved hepatitis B infection.

Screen patients for hepatitis B infection before initiating immunosuppressive (e.g., prolonged) treatment with Dexamethasone. For patients who show evidence of hepatitis B infection, recommend consultation with physicians with expertise in managing hepatitis B regarding monitoring and consideration for hepatitis B antiviral therapy.

Fungal Infections

Corticosteroids, including Dexamethasone, may exacerbate systemic fungal infections; therefore, avoid Dexamethasone use in the presence of such infections unless Dexamethasone is needed to control drug reactions. For patients on chronic Dexamethasone therapy who develop systemic fungal infections, Dexamethasone withdrawal or dosage reduction is recommended.

Amebiasis

Corticosteroids, including Dexamethasone, may activate latent amebiasis. Therefore, it is recommended that latent amebiasis or active amebiasis be ruled out before initiating Dexamethasone in patients who have spent time in the tropics or patients with unexplained diarrhea.

Strongyloides Infestation

Corticosteroids, including Dexamethasone, 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.

Cerebral Malaria

Avoid corticosteroids, including Dexamethasone, in patients with cerebral malaria.

Kaposi's Sarcoma

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 of Kaposi's sarcoma.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical, and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Appropriate antimicrobial therapy should accompany glucocorticoid therapy when necessary e.g. in tuberculosis and viral and fungal infections of the eye.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Special precautions

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);
- 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.

Paediatric population

Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible.

Dexamethasone has been used 'off label' to treat and prevent chronic lung disease in preterm infants. Clinical trials have shown a short term benefit in reducing ventilator dependence but no long term benefit in reducing time to discharge, the incidence of chronic lung disease or mortality. Recent trials have suggested an association between the use of dexamethasone in preterm infants and the development of cerebral palsy. In view of this possible safety concern, an assessment of the risk/benefit ratio should be made on an individual patient basis.

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.

This medicine contains less than 1mmol sodium (23mg) per dose, that is to say essentially «sodium-free».

Methylparaben and Propylparaben may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Sodium metabisulphite may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin, rifabutin, ephedrine, carbamazepine, phenylbutazone, phenobarbital, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Dexamethasone is a moderate inducer of CYP3A4. Co-administration of dexamethasone with other drugs that are metabolized by CYP3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

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.

The effects of anticholinesterases are antagonised by corticosteroids in myasthenia gravis.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives, cardiac glycosides and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. There may be interaction with salicylates in patients with hypoprothrombinaemia.

4.6 Fertility, pregnancy and lactation

The ability of corticosteroids to cross the placenta varies between individual drugs, however, dexamethasone readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of corticosteroids including dexamethasone to women at risk for late preterm delivery.

As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Lactation

Corticosteroids may pass into breast milk, although no data are available for dexamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Local adverse reactions include post-injection flare, and a painless destruction of the joint reminiscent of Charcot's 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 (see section 4.4).

Local injection of glucocorticoid may produce systemic effects.

The SOC Cardiac Disorders with a frequency not known:

Hypertrophic cardiomyopathy in prematurely born infants (see section 4.4).

Endocrine/metabolic

Suppression of the hypothalamic-pituitary-adrenal axis, premature epiphyseal closure, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea, Cushingoid faces, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for anti-diabetic therapy, negative protein and calcium balance, increased appetite.

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 (see section 4.4).

Musculoskeletal

Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture Proximal myopathy.

Fluid and electrolyte disturbance

Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis.

Neuropsychiatric

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.

Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal, aggravation of epilepsy, psychological dependence.

Ophthalmic

Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases, chorioretinopathy (see also section 4.4).

Eye disorders

Vision, blurred (see also section 4.4).

Gastrointestinal

Dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, candidiasis.

Dermatological

Impaired healing, skin atrophy, bruising, telangiectasia, striae, increased sweating and acne.

General

Hypersensitivity, including anaphylaxis and angioedema, have been reported. Leucocytosis. Thromboembolism.

A transient burning or tingling sensation mainly in the perineal area following intravenous injection of large doses of corticosteroid phosphates.

Withdrawal symptoms and signs

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4).

A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Arpimed "LLC" by going to www.arpimed.com and fill out the appropriate form "Report an adverse reaction or inefficiency of drug". Hotline number: (+374 55) 05 79 86. And by using Center of Drug and Medical Technology Expertise "SNPO", going to the site: www.pharm.am in "Report about adverse effect of medicine" section and fill out the "Report of adverse reaction or manufacturing problem of medicinal product". Hotline numbers: +37410200505; +37496220505.

4.9 Overdose

It is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to the indication and patient requirements. Massive i.v. corticosteroid doses given as a pulse in emergencies are relatively free from hazardous effects.

Exaggeration of corticosteroid related adverse effects may occur. Treatment should be asymptomatic and supportive as necessary.

5. PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties

ATC code: H02AB02.

Pharmacotherapeutic Group: Glucocorticoids

Dexamethasone is a synthetic adrenocorticoid with approximately a 7 times higher anti-inflammatory potency than prednisolone and 30 times that of hydrocortisone. Adrenocorticoids act on the HPA at specific receptors on the plasma membrane. On other tissues the adrenocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors which enter the cell nucleus and stimulate protein synthesis.. Adrenocorticoids have anti-allergic, antitoxic, antishock, antipyretic and immunosuppressive properties. Dexamethasone has only minor mineralocorticoid activities and does therefore, not induce water and sodium retention.

5.2 Pharmacokinetic properties

After administration of Dexamethasone Injection, dexamethasone sodium phosphate is rapidly hydrolysed to dexamethasone. After an iv dose of 20mg dexamethasone plasma levels peak within 5 minutes. Dexamethasone is bound (up to 77%) by plasma proteins, mainly albumin. There is a high uptake of dexamethasone by the liver, kidney and adrenal glands. Metabolism in the liver is slow and excretion is mainly in the urine, largely as unconjugated steroids. The plasma half life is 3.5-4.5 hours but as the effects outlast the significant plasma concentrations of steroids the plasma half-life is of little relevance and the use of biological half life is more applicable. The biological half life of dexamethasone is 36-54 hours, therefore dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desirable.

5.3 Preclinical safety data

In animal studies, cleft palate was observed in rats, mice, hamsters, rabbits, dogs and primates; not in horses and sheep. In some cases these divergences were combined with defects of the central nervous system and of the heart. In primates, effects in the brain were seen after exposure. Moreover, intra-uterine growth can be delayed. All these effects were seen at high dosages.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Creatinine,
Sodium citrate,
Sodium metabisulfite,
Methylparaben,
Propylparaben,
Sodium hydroxide,
Water for injection.

6.2 Incompatibilities

Dexamethasone sodium phosphate is physycally incompatible with daunorubicin, doxorubicin and vancomycin and should not be admixed with solutions containing these drugs. Also incompatible with doxapram HCl and glycopyrrolate in syring.

6.3 Shelf life

3 years.

6.4 Storage conditions

Store at a temperature not higher than 25°C, in original pack, out of the reach of children.

6.5 Presentation

5 ampoules with 1 ml sterile solution in PVC- container. 2 containers with leaflet inserted in cardboard box.

6.6 Special precautions for disposal and other handling

Dexamethasone solution for injection may be diluted with the following solutions for injection or infusion:

Sodium Chloride 0.9% infusion

Glucose 5% Infusion

Compound Sodium Lactate Infusion

Hartmann's Solution for Injection

Ringer-Lactate Solution for Injection

Ringer's Solution for injection

Sorbitol 5% Injection

Invert Sugar 10% Injection

Rheomacrodex

Using these infusion fluids, Dexamethasone solution for injection can also be injected into the infusion line without causing precipitation of the ingredients. (See also section 4.2).

For single use only.

Discard any unused solution after use.

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

The product should only be used when the solution is clear and particle free.

7. MANUFACTURER

“Arpimed” LLC

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8. MARKETING AUTHORIZATION HOLDER

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