

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dexamethasone 3.8 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each one ml contains 3.8 mg dexamethasone (as sodium phosphate) which is equivalent to 5.0 mg dexamethasone sodium phosphate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Colourless aqueous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dexamethasone solution for injection can be used for all forms of general and local glucocorticoid injection therapy and all acute conditions in which intravenous glucocorticoids may be life-saving.

4.2 Posology and method of administration

Dosage

Note: All dose recommendations stated in this section are expressed as mg dexamethasone base.

In general, glucocorticoid dosage depends on the severity of the condition and response of the patient. Under certain circumstances, for instance in stress,

extra dosage adjustments may be necessary. If no favourable response is noted within a couple of days, glucocorticoid therapy should be discontinued.

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 dosages 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 tumours can be counteracted by continuous treatment.

For local treatment, the following dosages can be recommended:

- intra-articular: 1.6 - 3 mg large joints
0.6 - 0.8 mg small joints
- intrabursally: 1.6 - 3 mg;
- in tendon sheaths: 0.3 - 0.8 mg

The frequency of these injections may vary from every 3 - 5 days to every 2 - 3 weeks. For rectal drip in cases of ulcerative colitis: 4 mg diluted in 120 ml saline.

Suggested doses for children

Dosage requirements are variable and may have to be changed according to individual needs. Usually 0.2 mg/kg to 0.4 mg/kg of body weight daily.

Method of administration

Dexamethasone solution for injection may be administered intravenously, subcutaneously, intramuscularly, by local injection or as a rectal drip. 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.

In post-marketing experience tumour lysis syndrome (TLS) has been reported very rarely in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS should be monitored closely and appropriate precautions 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, 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.

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.

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.

Anti-inflammatory/Immunosuppressive effects and Infection

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.

Measles. Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs; prophylaxis with intramuscular normal immunoglobulin may be needed.

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

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)
- 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.

Use in children

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 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.

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.

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

Pregnancy

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 (see also section 5.3). 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. 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

Not relevant.

4.8 Undesirable effects

Side-effects

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 (see section 4.4).

Local injection of glucocorticoid may produce systemic effects.

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.

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, has 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.

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 IV 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 PROPERTIES

5.1 Pharmacodynamic properties

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 solution for injection, dexamethasone sodium phosphate is rapidly hydrolysed to dexamethasone. After an IV dose of 20 mg 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

Glycerol (E422)
Disodium edetate
Water for injections
Sodium hydroxide (E524) **or**
Phosphoric acid (E338)

6.2 Incompatibilities

None known.

6.3 Shelf life

As packaged for sale

2 years

The product should be used immediately after first opening.

Following dilution with infusion fluids (see section 6.6):

Chemical and physical in-use stability of dilutions has been demonstrated for at least 24 hours, at 25°C (room temperature)

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale

Store in a refrigerator (2 °C - 8 °C). Do not freeze. Store in the original package.

Following dilution with infusion fluids:
See section 6.3.

6.5 Nature and contents of container

2 ml colourless glass vial containing 1 ml of solution. Available in cartons of 1 or 10 vials.

Not all pack sizes may be marketed.

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 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 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited,
3016 Lake Drive,

Citywest Business Campus,
Dublin 24,
Ireland

8 MARKETING AUTHORISATION NUMBER

PL 39699/0060

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

31 March 1989 (Review)/ 18 June 2010

10 DATE OF REVISION OF THE TEXT

30/04/2014