SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dexamethasone Kern Pharma 4 mg/ml solution for injection, Generic medicinal product

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per 1 ml (per ampoule):
Dexamethasone (INN) phosphate 4 mg (as dexamethasone sodium phosphate, 4.37 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Transparent solution

pH: 7-8.5

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

By intramuscular or intravenous route

Dexamethasone Kern Pharma is indicated in the treatment of:

- Endocrine diseases such as nonsuppurative thyroiditis, hypercalcaemia associated with cancer and congenital adrenal hyperplasia. Dexamethasone, in combination with a mineralcorticoid, may be very useful in primary or secondary adrenocortical insufficiency, although cortisone and hydrocortisone are the drugs of choice.
- Severe or disabling allergic conditions resistant to conventional treatments, as in: bronchial asthma, contact or atopical dermatitis, seasonal or perennial allergic rhinitis, hypersensitivity reactions to drugs.
- Serious inflammatory and allergic processes, acute and chronic, affecting the eyes, such as: iritis and iridocyclitis, chorioretinitis, choroiditis and diffuse posterior uveitis, optical neuritis, allergic conjunctivitis, queratitis, allergic marginal corneal ulcers.
- Systemic treatment in critical periods of ulcerative colitis and regional enteritis.
- Dermatological diseases (pemphigus, Stevens-Johnson syndrome, exfoliative dermatitis [bullous herpetiform or severe seborrheal], severe psoriasis and mycosis fungoides), respiratory (symptomatic sarcoidosis, berylliosis, Loeffler's syndrome not treatable by other means, aspirative pneumonitis, etc.) and haematological (acquired [autoimmune] haemolytic anaemia, idiopathic thrombocytopenic purpura in adults by the intravenous route [the intramuscular route is contraindicated], secondary thrombocytopenia in adults, erythroblastopenia and congenital hypoplastic anaemia).
- Idiopathic nephrotic syndrome (without uraemia) or that caused by lupus erythematosus.
- Cerebral oedema associated with brain tumour, primary or metastatic, craniotomy or cranial lesion.

As a coadjuvant treatment in the short term during acute episodes or exacerbations of rheumatic diseases: arthritis (rheumatoid, acute gouty, psoriatic, etc.), post-traumatic osteoarthritis, ankylosing spondylitis, epicondylitis, tenosynovitis, bursitis, etc.

During an exacerbation or as maintenance therapy, in some cases of systemic lupus erythematosus and acute rheumatic carditis.

For the palliative treatment of leukaemia and lymphomas in adults and acute leukaemia in children.

By intraarticular or intralesional route or injection in soft tissues

As combined short-term therapy in acute episodes or exacerbations of: osteoarthritis synovitis, rheumatoid arthritis, acute or subacute bursitis, acute gouty arthritis, epicondylitis, unspecific acute tenosynovitis, post-traumatic osteoarthritis.

By intralesional injection in inflammatory, infiltrated, hypertrophic and localised lesions of the lichen planus, plaque psoriasis, granuloma annulare and lichen simplex chronicus (neurodermatitis). Keloids. Discoid lupus erythematosus. Necrobiosis lipoidica diabeticorum. Alopecia areata. It may be useful in cystic tumours of an aponeurosis or tendon.

4.2. Posology and method of administration

Posology

Dexamethasone Kern Pharma 4 mg/ml solution for injection contains 4 mg of dexamethasone per ampoule by the intravenous, intramuscular, intraarticular and intralesional routes and for injection in soft tissues. It may be applied directly or be added to a solution of physiological saline solution or glucose solution and administered through a drip.

DOSING REQUIREMENTS ARE VARIABLE AND SHOULD BE INDIVIDUALISED BASED ON THE DISEASE AND PATIENT RESPONSE

Intravenous and intramuscular route

As with other steroids, provided the condition allows it, the most appropriate posology of Dexamethasone Kern Pharma 4 mg/ml solution for injection is:

a) Single daily dose (daytime), since this causes less alteration of the hypothalamic-pituitary-adrenal (HPA) axis.

b) Single dose every second day to prevent iatrogenic Cushing's Syndrome and suppression of the HPA axis.

The initial dose of Dexamethasone Kern Pharma 4 mg/ml solution for injection varies between 0.5 and 9 mg a day, depending on the disease being treated. Doses of less than 0.5 mg may be sufficient in less severe processes, while severe diseases may require more than 9 mg. The initial dose should be maintained or adjusted until the patient response is satisfactory and, if no suitable clinical response is obtained after a reasonable period of time, it should be discontinued and the patient's treatment changed.

Once an initial favourable response has been obtained, a suitable maintenance dose should be established; for this purpose, the initial dose should be reduced in small amounts until the lowest dose that maintains a suitable clinical response is obtained. The patients should be observed meticulously to detect signs that they may require a dose titration, such as changes in the clinical status resulting from disease remissions or exacerbations, individual drug response and the effect of stress (for example surgery, infection, trauma, etc.). It may be necessary to increase the dose temporarily during periods of stress.

If, after several days of treatment, the administration of the drug has to be suspended, it should be withdrawn gradually.

For the treatment of cerebral oedema, Dexamethasone Kern Pharma 4 mg/ml solution for injection will be given intravenously and once only at a dose of 2 ampoules (8 mg) and will then be continued with one ampoule (4 mg) every 6 hours, intramuscularly, until the cerebral oedema symptoms have remitted. Response is normally achieved after 12-24 hours and dosage may be reduced after two to four days and gradually withdrawn over a period of 5 to 7 days.

For the palliative treatment of patients with inoperable brain tumours, maintenance treatment with 2 mg (half an ampoule of Dexamethasone Kern Pharma 4 mg/ml solution for injection) two or three times a day may be effective.

In acute allergic disorders or in exacerbations of chronic allergic processes, Dexamethasone Kern Pharma 4 mg/ml solution for injection may be given intramuscularly as follows: 1 or 2 ampoules the first day, one ampoule on days two to four and half an ampoule on days five to seven.

Paediatric population

In children, the recommended daily dose is 0.08-0.3 mg/kg or 2.5-10 mg/m²

Method of administration.

Intraarticular and intralesional route and injection in soft tissues

This method of administration is used when the affected joints or areas are limited to one or two sites. Dosage and frequency of administration vary depending on status and administration site; the usual dose is 0.2 to 6 mg and the frequency from once every 3-5 days to once every 2-3 weeks. The repeated administration of intraarticular injections may give rise to articular tissue lesions.

Some recommended doses are as follows:

Injection site	Dose
Large joints (knee)	2-4 mg
Small joints (phalangeal, temporo-mandibular)	0.8-1 mg
Bursae	2-3 mg
Tendinous sheaths	0.4-1 mg
Infiltration of soft tissues	2-6 mg
Nodes	1-2 mg

Dexamethasone Kern Pharma 4 mg/ml solution for injection is particularly recommended for combined use with a less soluble and longer-acting corticosteroid in intraarticular injections and in soft tissues.

Posology must be adjusted in patients with kidney and liver failure.

4.3. Contraindications

The use of Dexamethasone Kern Pharma 4 mg/ml solution for injection is contraindicated in patients with hypersensitivity to any of its ingredients. Anaphylactoid and hypersensitivity reactions have been reported following the injection of dexamethasone. These reactions, although they occur on rare occasions in patients with previous allergic drug reactions, are more common.

Corticosteroids can mask some signs of infection or even induce the appearance of new infections or worsen existing ones. Therefore, the use of Dexamethasone Kern Pharma 4 mg/ml solution for injection is contraindicated, unless the patient receives suitable chemotherapy treatment and undergoes strict medical monitoring, in systemic fungal infections, disseminated tuberculosis, latent tuberculosis or with tuberculin reactivity in patients with infestations or suspected digestive parasite infestations, herpes, measles and varicella.

The administration of vaccines with live viruses, including smallpox, is contraindicated in people receiving immunosuppressive doses of corticosteroids. In the event of bacterial vaccines or inactivated viruses, corticosteroids can prevent the expected immunological response of a vaccination (increase in serum antibodies). Nevertheless, immunisation procedures may be undertaken in patients receiving corticosteroids as replacement therapy, for example in Addison's disease.

Similarly, prolonged treatment with dexamethasone is not recommended in congestive heart disease, myasthenia gravis, peptic ulcer or oesophagitis, diabetes and ocular herpes simplex.

4.4. Special warnings and precautions for use

Corticosteroids should be used with caution in patients with: unspecific ulcerative colitis, with probability of imminent perforation, abscess or other pyogenic infection, diverticulitis, recent intestinal anastomoses, active or latent peptic ulcer, renal failure, hypertension, osteoporosis and myasthenia gravis. In patients on high doses of corticosteroids, signs of peritoneal irritation following gastrointestinal perforation may be minimal or not present. Fatty embolism is a complication that may present during hypercorticism.

In treatment with corticosteroids, the lowest possible dose should always be used until the pathological situation is controlled; the dose should be down-titrated gradually, since withdrawal may give rise to the appearance of symptoms such as fever, myalgia, arthralgia, malaise, etc., typical of acute adrenocortical failure from withdrawal syndrome. This may even occur in patients without evidence of adrenal insufficiency.

In patients with hypothyroidism or in patients with cirrhosis, corticosteroids present an increased pharmacological effect. Their use in stressful situations (infections, trauma, surgery, etc.) may require an increase in the dose.

Patients susceptible to becoming infected with varicella or measles and who are being treated with immunosuppressive doses of corticosteroids should be carefully warned to avoid exposure to these germs.

The joint administration of antibiotics and corticosteroids should be controlled since the infection may be disseminated if the causal germ is not sensitive to the antibiotic used.

When high doses are given, the administration of antacids between meals may help to prevent peptic ulcer.

The intraarticular route of a corticosteroid given by injection can produce systemic and local effects.

The presence of articular effusion during treatment with corticosteroids requires examination to rule out a septic process. A marked increase in pain accompanied by local swelling, extensive restriction of articular mobility, fever and malaise is suggestive of septic arthritis. If this complication occurs, and the diagnosis of articular infection is confirmed, appropriate antimicrobial treatment should be initiated.

The injection of a corticosteroid in an infected site should be avoided. Corticosteroids should also not be injected in unstable joints. Frequent intraarticular injection may give rise to articular tissue lesions.

It should be borne in mind that intramuscular administration presents a slower level of absorption.

This medicinal product contains less than 23 mg (<1 mmol) of sodium per dose; i.e., it is essentially "sodium-free".

As it contains propyl parahydroxybenzoate and methyl parahydroxybenzoate, it may cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm (sudden sensation of suffocation).

In postmenopausal women, Dexamethasone Kern Pharma may reduce the intestinal absorption of calcium and the activity of bone-forming cells, which could exacerbate existing osteoporosis.

Children and the elderly

The chronic use of dexamethasone involves the risk of adrenal suppression and retarded growth, hence body growth and development should be evaluated carefully during use in children.

In the elderly it should be remembered that corticosteroids may inhibit the digestive absorption of calcium and osteoblastic activity, which could exacerbate an incipient or ongoing osteoporosis. They may also increase hydrosaline retention and blood pressure.

Athletes

Athletes are informed that this medicinal product may give a positive result in a doping test.

4.5. Interaction with other medicinal products and other forms of interaction

Phenytoin, phenobarbital, adrenaline and rifampicin may increase the metabolic clearance of corticosteroids, leading to reductions in their blood levels and a reduction in their pharmacological activity; requiring an adjustment in the corticosteroid dose. These interactions may interfere with the dexamethasone suppression test, whereby the results obtained in these situations should be interpreted with caution during the administration of these drugs.

Dexamethasone may reduce plasma levels of albendazole, with a possible inhibition of its effect through the induction of its hepatic metabolism.

Ephedrine may reduce dexamethasone plasma levels, with possible loss of antiasthmatic control.

False negatives have been reported in the dexamethasone suppression test in patients treated with indometacin; these results should be interpreted with caution.

Acetyl salicylic acid, due to its hypoprothrombinic activity, should be used with caution during treatment with corticosteroids.

Prothrombin time should be checked frequently in patients being given coumarin anticoagulants or indandione derivatives with corticosteroids, since the latter alter anticoagulant response. Different studies have demonstrated that they normally inhibit the response to coumarin, although there are studies in which boosting occurs.

When corticosteroids are given concomitantly with potassium-sparing diuretics, patients should be examined frequently in order to avoid the development of hypokalaemia.

Glucocorticoids may increase blood glucose concentrations. It may be necessary to adjust the dosage of oral glycaemia-lowering agents or insulin or glucocorticoids when administered jointly with some of these medicinal products.

Dexamethasone reduces the effects of antidiabetics and boosts the hypokalaemia of different diuretics and cardiotonic glycosides. The action of corticosteroids increases if it is combined with oestrogens and falls if used with aminoglutethimide, carbamazepine, phenytoin or rifampicin. With indometacin there is mutual boosting of toxicity, and with isoniazid a reduction in the plasma levels of the latter.

This medicinal product may alter values in:
- Blood: increased cholesterol and glucose and reduction of calcium, potassium and thyroid hormones.
- Urine: increase in glucose.
- Skin tests: tuberculin and patch tests for allergy.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no controlled studies on the use of Dexamethasone Kern Pharma 4 mg/ml solution for injection in pregnant women.

The studies performed with corticosteroids in experimental animals have shown congenital alterations (microcephalia, hepatomegaly, reduction in adrenal medulla size and thymus), although some preliminary studies had suggested that the use of corticosteroids during pregnancy was associated with a 1% incidence of cleft palate in the newborn, subsequent and more elaborate studies have not established this relationship. (See section 5.3)

In pregnant women, the benefit-risk ratio should be evaluated, since the therapeutic benefit of this drug may occasionally be superior to the potential teratogenic risk, and its use in pregnancy may be justified only under strict medical supervision, since there are many clinical cases that support the use of corticosteroids during pregnancy, provided that they are therapeutically indispensable (hormone replacement treatment, etc.). Dexamethasone has been used in pre-term partum (26-34 weeks) to improve pulmonary maturity in new-borns.

Children born of mothers who have been treated with corticosteroids during pregnancy should be monitored carefully to detect signs of hypoadrenalism.

Lactation

Dexamethasone is excreted in the mother’s milk and therefore prolonged treatments with high doses may affect the infant’s adrenal function. It may also interfere with growth and with the endogenous production of corticosteroids or cause other adverse effects in the infant, so it is recommended that the infant be monitored.

4.7. Effects on the ability to drive and use machines

No signs of effects on the ability to drive vehicles and use machines that require special care have been described.

4.8. Undesirable effects

In most cases, the undesirable effects are a prolongation of the pharmacological action and are more frequent with high doses and in prolonged treatments.

Common (between ≥1/100 and ≤1/10 of patients):

Immune system disorders: reduction in resistance to infections, oropharyngeal candidiasis.
Endocrine disorders: hyperglycaemia, adrenocortical insufficiency.
At high doses: signs of adrenal hyperactivity (Cushing's syndrome) with acneiform eruptions.
Metabolism and nutrition disorders: polyphagia.
Eye disorders: cataracts.
Vascular disorders: at high doses, hot flashes.
Gastrointestinal disorders: at high doses: gastric ulcer.
Skin and subcutaneous tissue disorders: delayed wound healing, local allergic reaction.

At high doses: hirsutism, cutaneous hyperpigmentation, scleroderma.
Musculoskeletal and connective tissue disorders: osteoporosis, bone fragility.
With prolonged treatments: muscular atrophy.

Uncommon (between ≥1/1,000 and ≤1/100 of patients):

Blood and lymphatic system disorders: Lymphopenia, eosinopenia.
Immune system disorders: generalised allergic reaction.
Endocrine disorders: amenorrhea.
Metabolism and nutrition disorders: hypokalaemia, acute pancreatitis.
Nervous system disorders: intracranial hypertension, neurological alterations, psychotic states.
Cardiac disorders: heart failure.
Vascular disorders: thromboembolism, oedema, hypertension.
Skin and subcutaneous tissue disorders: perspiration.
Musculoskeletal and connective tissue disorders: myasthenia
General disorders and administration site conditions: With the rapid intravenous administration of high doses: allergic reactions and local infection at the injection site, generalised anaphylaxis, reddening of face or cheeks, irregular heartbeats or palpitations, convulsive crises.

They occur mainly during long-term use and require medical care: acne or other skin problems, avascular necrosis, Cushing's syndrome, oedema, endocrine imbalance, gastrointestinal irritation, hypokalaemia syndrome, osteoporosis or bone fractures, pancreatitis, peptic ulcer or intestinal perforation, scarring at the injection site, steroid myopathy, striae, tendon rupture. Local injection, unusual bruising, wounds that do not heal.

In the event of the appearance of undesirable effects, treatment should be suspended and the pharmacovigilance systems notified.

The treatment should be suspended immediately if the patient has any episode of adrenal hyperactivity, for example: acne, hirsutism, cutaneous hyperpigmentation, hot flashes and scleroderma.

4.9. Overdose

Acute intoxication or death by overdose may occur in a very low percentage of patients. The symptoms that may be observed are anxiety, depression, mental confusion, digestive spasms or haemorrhages, hyperglycaemia, high blood pressure and oedema. In these cases, the administration of phenobarbital is indicated, which reduces the half-life of dexamethasone by 44%, as well as symptomatic and support treatment, including oxygen therapy, maintenance of body temperature, adequate fluid intake and control of electrolytes in serum and urine. Digestive haemorrhage symptoms should be treated in the same way as a peptic ulcer.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Dexamethasone Kern Pharma 4 mg/ml solution for injection belongs to the H02AB02 therapeutic group.

Dexamethasone is a fluorinated, long-acting, high-potency, anti-inflammatory and immunosuppressive corticosteroid with low mineralocorticoid activity. Glucocorticoids cause profound and varied metabolic effects. They also modify immune response to different stimuli.

This drug inhibits the synthesis of prostaglandins and leukotrienes, substances that mediate in the vascular and cell processes of inflammation and immunological response. Therefore, they reduce vasodilation and the liquid exudate typical of inflammatory processes, leukocyte activity, neutrophil aggregation and degranulation, the release of hydrolytic enzymes by lysosomes, etc. Both actions are due to the inhibition of the synthesis of phospholipase A_2, the enzyme responsible for releasing the polyunsaturated fatty acids that are precursors of prostaglandins and leukotrienes.

Dexamethasone, like the rest of the glucocorticoids, binds to the cytoplasmic glucocorticoid receivers, activating them. As a result, different neutral endopeptidases, plasminogen activator inhibitors, lipocortin, etc. are mobilised.

Glucocorticoids reduce the stability of certain RNA messenger molecules, altering gene transcription. The genes affected by this action include the synthesis of collagenase, elastase, plasminogen activator, type II cyclooxygenase, cytokines and chemokines.

Other actions

Pharmacological doses of exogenous corticosteroids cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis through a negative feedback mechanism.

Glucocorticoids stimulate protein catabolism and induce the enzymes responsible for the metabolism of the amino acids.

Glucocorticoids increase the availability of glucose for different actions that cause the hepatic reserves of glycogen, concentrations of glucose in blood and resistance to insulin.

Glucocorticoids increase lipolysis and mobilise the fatty acids of the adipose tissue, leading to an increase in fatty acid plasma concentrations. They also reduce bone formation and increase its resorption.

Dexamethasone, the active substance of Dexamethasone Kern Pharma 4 mg/ml solution for injection, is 30 times more potent than cortisone, 25 times more potent than hydrocortisone, 6 times more potent than prednisone and prednisolone and 5 times more potent than methylprednisolone and triamcinolone.

5.2. Pharmacokinetic properties

Dexamethasone is a long-acting corticosteroid, since its effects are maintained for up to 72 hours, its total clearance varies between 2.8 and 3.5 mg/minute/kg, elimination half-life is 3-4 hours (limits of 3 to 6 hours for adults, 2.8-7.5 hours for 8-16 years and 2.3-9.5 hours for under 2 years) and its biological half-life is 36-54 hours

Following intramuscular administration, peak serum levels are reached within one hour, it is widely distributed in the organism with a degree of plasma protein binding of 70%, it crosses the placental and blood-milk barriers, the volume of distribution is 2 l/kg, it is metabolised in the liver (hydroxylation) and is eliminated in urine, 8% in unchanged form and to a lesser extent in bile.

5.3. Preclinical safety data

Dexamethasone is a drug that acts on the hypothalamic-pituitary-adrenal (HPA) axis, hence it may give rise to Cushing's syndrome and osteoporosis, among others. Nevertheless, this may occur after the prolonged use of relatively high doses.

Although its teratogenic and embryotoxic effect has been detected in different animal species, there are no studies that make it possible to link these facts with the human species. Dexamethasone has not been shown to have carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Methyl parahydroxybenzoate (E-218)
Propyl parahydroxybenzoate (E-216)
Disodium edetate
Sodium citrate (E-331i)
Sodium hydroxide 524)
Water for injection

6.2. Incompatibilities

Different types of incompatibilities have been described in the association of different concentrations of dexamethasone with the following drugs:
Amikacin
Chlorpromazine
Daunorubicin
Diphenhydramine
Doxapram
Doxorubicin
Gallium nitrate
Glycopyrronium bromide
Hydromorphone
Idarubicin
Lorazepam
Metaraminol
Ondansetron
Prochlorperazine
Vancomycin

6.3. Shelf-life

3 years

6.4. Special precautions for storage

Dexamethasone Kern Pharma 4 mg/ml solution for injection is heat-sensitive and consequently should not be heated in an autoclave.

Do not freeze.
Store in the original container to protect it from the light.

6.5. Nature and contents of container

Container with three type-I glass ampoules containing 1 ml of solution for injection (4 mg of Dexamethasone phosphate).
Other presentations: Clinical container containing 100 ampoules.

6.6. Special precautions for disposal and other handling

Only transparent solutions free of turbidities and precipitates should be used.
Any unused product or waste material that has been in contact with the product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KERN PHARMA, S.L.
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Venus, 72
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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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