1. NAME OF THE MEDICINAL PRODUCT

Dexamethasone Rompharm 4 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains: dexamethasone phosphate 4 mg (as dexamethasone sodium phosphate, 4.37 mg).

Excipients with known effect: sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

By intramuscular or intravenous routeDexamethasone Rompharm is indicated in the treatment of:

- Endocrine diseases such as nonsuppurative thyroiditis, hypercalcaemia associated with cancer and congenital adrenal hyperplasia.
- Allergy: 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.
- Ophtalmic: 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, allergic marginal corneal ulcers.
- Inflammatory Bowel dis.: Systemic treatment in exacerbations of ulcerative colitis and regional enteritis.
- Dermatological diseases (pemphigus, Stevens Johnson syndrome, exfoliative dermatitis, severe psoriasis and mycosis fungoides)
- Respiratory diseases (symptomatic sarcoidosis, berylliosis, Loeffler's syndrome)
- Haematological: acquired (autoimmune) haemolytic anaemia, idiopathic thrombocytopenic purpura in adult, pure red cell aplasia
- Nephrotic syndrome of the idiopathic type or that due to lupus erythematosus
- Cerebral oedema caused by brain tumor, neurosurgery, brain abscess, bacterial meningitis
- Collagen diseases: Active rheumatoid arthritis with severe progressive course, fast destructive remitting forms and / or extra-articular manifestations, Juvenile idiopathic arthritis with severe systemic-onset form (Still's disease) or locally with no control, rheumatic fever with carditis, dermatomyositis, polymyositis, SLE, temporal arteritis.

- Infectious Diseases: Bacterial meningitis – adjunct to antibiotics in suspected Pneumococcal meningitis and TB meningitis. Severe infectious diseases with toxic states (eg tuberculosis, typhoid, brucellosis;. Only with simultaneous anti-infective therapy)
- Fetal lung maturation
- Chemotherapy – associated nausea and vomiting
- Multiple Myeloma – part of chemotherapy protocols (eg VAD)
- Prevention and treatment of acute mountain sickness/HACE

4.2. Posology and method of administration

Posology

Dexamethasone Rompharm contains 4 mg of dexamethasone per ml for intravenous and intramuscular injection. It can be applied directly or it can be added to the diluents mentioned in section 6.6 and given through a drip.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

Intravenous route
Idiopathic thrombocytopenic purpura in adult by the intravenous route (the intramuscular route is contraindicated),

Intravenous and intramuscular route

As with other steroids, disease permitting, the most suitable posology of Dexamethasone Rompharm is:

a) Single daily dose (with diurnal rhythm), since this causes less disruption 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 dosage of Dexamethasone Rompharm varies from 0.5 to 9 mg a day, depending on the disease being treated. In less severe diseases, doses lower than 0.5 mg may suffice, while in more severe diseases doses higher than 9 mg may be required. The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue therapy and transfer the patient to another therapy.

After a favourable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response. Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness and the effect of stress (e.g., surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily.

If the drug is to be stopped after a few days of treatment, it should be withdrawn gradually.

For the treatment of cerebral oedema, Dexamethasone Rompharm
will be administered intravenously and once only at a dose of
8 mg and will then be continued with 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.

In acute allergic disorders or in exacerbations of chronic allergic processes Dexamethasone Rompharm may be given
intramuscularly as follows: 4 mg or 8 mg the first day, 4 mg on days two to four and 2 mg 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.

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

4.3. Contraindications

The use of Dexamethasone Rompharm is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1
. Anaphylactoid and hypersensitivity reactions have been reported following the injection of dexamethasone. These reactions, although they occur on rare occasions in patients with a history of allergy to any drug, are more common.

Corticosteroids may mask some signs of infection or even induce the appearance of new infections or worsen existing ones. Therefore, the use of Dexamethasone Rompharm is contraindicated, unless the patient receives suitable chemotherapy and is under strict medical supervision, in systemic fungal infections, disseminated tuberculosis, latent tuberculosis or with tuberculin reactivity, in patients with a known or suspected parasitic infection of the GI tract, herpes, measles and chickenpox.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered, corticosteroids can prevent the expected immunological response of the vaccination (increase in serum antibodies) from occurring. However, immunization procedures may be undertaken in patients receiving corticosteroids as replacement therapy, e.g., for 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.

Idiopathic thrombocytopenic purpura in adult is contraindicated by the intramuscular route.

4.4. Special warnings and precautions for use

Steroids should be used with caution in patients with: nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, recent intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving high doses of corticosteroids may be minimal or absent. Fat embolism is a possible complication during hypercorticism.

In treatment with corticosteroids, the lowest possible dose should always be used until the condition under treatment is controlled; subsequent reduction in dosage must be gradual, since withdrawal may give rise to the appearance of symptoms such as fever, myalgia, arthralgia, malaise, etc. typical of acute adrenocortical insufficiency from withdrawal syndrome. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis. Their use in stressful situations (infections, trauma, surgery, etc.) may require a dose increase.

Patients susceptible to becoming infected with chickenpox or measles and who are on immunosuppressant doses of corticosteroids should be carefully warned to avoid exposure to these germs.

Co-administration of antibiotics and corticosteroids should be controlled since the infection may be disseminated if the causative germ is not sensitive to the antibiotic used.

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

It should be noted that intramuscular administration presents a slower absorption rate.

This medicinal product contains up to 14.5mmol (or 334 mg) sodium per maximum single dose of the medicinal product (350 mg dexamethasone phosphate for a person with 70 kg bodyweight). To be taken into consideration by patients on a controlled sodium diet.

In post marketing experience tumor lysis syndrome (TLS) has been reported in patients with haematological malignancies following the use of dexamethasone alone or in combination with other chemotherapeutic agents. Patient 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.

In postmenopausal women, Dexamethasone Rompharm may reduce the intestinal absorption of calcium and the activity of bone-forming cells, which might worsen an existing osteoporosis.

Children and the elderly

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

In the elderly it should be remembered that corticosteroids may inhibit the absorption of calcium in the GI tract and osteoblast activity, which might exacerbate an incipient or established osteoporosis. They may also increase salt and water retention and blood pressure.

Athletes

Athletes are informed that this medicine may cause a positive result on 'anti-doping' tests.

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 cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

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

Phenytoin, phenobarbital, epinephrine and rifampicin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened pharmacological activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during 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 plasma levels of dexamethasone, with a possible loss of anti-asthma control.

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

Due to its hypoprothrombinemic activity, acetylsalicylic acid should be used with caution while on 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 shown that, usually, they inhibit response to coumarins, although there have been some studies where the response has been enhanced.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be examined frequently to avoid the development of hypokalaemia.

Glucocorticoids may increase blood glucose concentration; the dosage of oral hypoglycemic agents or insulin or glucocorticoid may have to be adjusted when given concomitantly with any of these medicines.

Dexamethasone reduces the effects of antidiabetic agents and enhances the hypokalaemia induced by different diuretics and cardiotonic glycosides. The action of corticosteroids is increased when combined with estrogens and decreased when used with aminoglutethimide, carbamazepine, phenytoin or rifampicin. With indomethacin there is mutual potentiation of toxicity, and with isoniazid there is a reduction in the plasma levels of isoniazid.

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.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no controlled studies on the use of Dexamethasone Rompharm in pregnant women.

Studies performed with corticosteroids in experimental animals have shown congenital abnormalities (microcephaly, enlarged liver, a decrease in the size of the adrenal medulla and the thymus gland), although some preliminary studies had suggested that the use of corticosteroids during pregnancy was associated with a 1% incidence of cleft palate in the new-born, subsequent and more elaborate studies have not been able to establish this association. (See section 5.3)

In pregnant women, the risk-benefit ratio should be evaluated, since the therapeutic benefit of this drug may eventually outweigh the potential teratogenic risk, and its use in pregnant women 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 therapy, etc.). Dexamethasone has been used in premature birth (26-34 weeks) to improve pulmonary maturity in new-borns.

Children born of mothers treated with corticosteroids during pregnancy should be monitored carefully for any signs of hypoadrenalism.

Breast-feeding

Dexamethasone is excreted in mother milk and, therefore, prolonged treatment with high doses may alter 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, hence infant monitoring is advised.

4.7. Effects on the ability to drive and use machines

No signs of effects on the ability to drive vehicles and use machines requiring special attention have been reported.

4.8. Undesirable effects

In most cases, the undesirable effects consist of prolonged pharmacological activity, and are more common with high doses and prolonged treatment.

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: cataract.
Vascular disorders: with high doses, hot flushes.
Gastrointestinal disorders: with high doses: gastric ulcer.
Skin and subcutaneous tissue disorders: delayed wound healing, local allergic reaction.

At high doses: hirsutism, skin hyperpigmentation, scleroderma.
Musculoskeletal and connective tissue disorders: osteoporosis, bone fragility.
With prolonged treatment: 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: amenorrhoea.
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: sweating.
Musculoskeletal and connective tissue disorders: myasthenia
General disorders and administration site conditions: With the rapid intravenous administration of high doses: allergic reactions and infection at the local injection site, generalised anaphylaxis, a reddening of the face or cheeks, irregular heartbeat or palpitations, convulsive seizures.

Unknown frequency (can not be estimated from the available data):
General disorders: Hiccups
Eye disorders: Chorioretinopathy; vision blurred (see also section 4.4.)

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, hypokalaemic 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.

Should the onset of any adverse effects be observed, treatment should be discontinued and pharmacovigilance systems should be notified accordingly.

Treatment must be discontinued immediately if the patient has any episode of adrenal hyperactivity, e.g.: acne, hirsutism, skin hyperpigmentation, hot flushes and scleroderma.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

www.sideeffects.health.co.il

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, spasms or GI bleeding, hyperglycaemia, high blood pressure and oedema. Administration of phenobarbital is indicated in these cases, since it reduces the half-life of dexamethasone by 44%, in addition to symptom and support treatment including oxygen therapy, maintenance of body temperature, adequate fluid intake and control of electrolytes in serum and urine. GI bleeding should be treated in the same way as a peptic ulcer.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Dexamethasone Rompharm belongs to the H02AB02 therapeutic group.

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

This medicine inhibits the synthesis of prostaglandins and leukotrienes, substances that mediate the vascular and cell processes involved in inflammation and immune response. They therefore reduce vasodilation and the fluid 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 all glucocorticoids, binds to cytoplasmic glucocorticoid receptors and activates 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 suppress the hypothalamic-pituitary-adrenal (HPA) axis through a negative feedback mechanism.

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

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

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

Dexamethasone, the active substance of Dexamethasone Rompharm, 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 ranges between 2.8 and 3.5 mg/minute/kg, its elimination half-life is 3-4 hours (limits of 3 to 6 hours for adults, 2.8-7.5 hours for 8-16 year olds and 2.3-9.5 hours for children less than 2 years old) 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 associate these facts in the human species. Dexamethasone has not been shown to have carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium citrate
Creatinine
Disodium edetate
Sodium hydroxide solution 1M (for pH adjustment)
Water for injections

6.2. Incompatibilities

Dexamethasone sodium phosphate is physically incompatible with daunorubicin, doxorubicin, vancomycin, diphenhydramine (with lorazepam and metoclopramide) and metaraminol bitartrate and should not be admixed with solutions containing these drugs. Different types of incompatibilities have been also reported in the mixture of different concentrations of dexamethasone with the following drugs: amikacin, chlorpromazine, gallium nitrate, hydromorphone, ondansetron, prochlorperazine. It is also incompatible with doxapram and glycopyrrolate in syringe and with ciprofloxacin, idarubicin and midazolam in Y-site injections (1:1 mixture).

6.3. Shelf-life

The expiry date of the product is indicated on the packaging materials.
After first opening: use immediately.
After dilution: Chemical and physical in-use stability after dilution has been demonstrated for 24 hours when stored below 25°C protected from light.
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.

6.4. Special precautions for storage

Store below 25°C. Store in the original package.

6.5. Nature and contents of container

Box with 10 ampoules of glass type I, brown; each ampoule contains 1 ml of solution for injection.
Box with 25 ampoules of glass type I, brown; each ampoule contains 1 ml of solution for injection.

Box with 100 ampoules of glass type I, brown; each ampoule contains 1 ml of solution for injection.
Box with 10 ampoules of glass type I, brown; each ampoule contains 2 ml of solution for injection.
Box with 25 ampoules of glass type I, brown; each ampoule contains 2 ml of solution for injection.
Box with 100 ampoules of glass type I, brown; each ampoule contains 2 ml of solution for injection.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Dexamethasone solution for injection can be diluted with the following infusion fluids:
Sodium Chloride 0.9% infusion
Glucose 5% Infusion
Ringer's Solution for injection

For single use only. Discard any unused solution after use. The product should only be used when the solution is clear and particle free.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

S.C. Rompharm Company S.R.L.,
1A Eroilor Street, 075100 Otopeni, Jud. Ilfov, Romania

8. MARKETING AUTHORIZATION NUMBER

166-10-35702-00

9. MARKETING AUTHORIZATION HOLDER

A.L.MEDI-MARKET Ltd.
3 Hakatif Street, Emek Hefer Industrial Park, 3877701

10. DATE OF REVISION OF THE TEXT

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