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/infusion

Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

By intramuscular or intravenous route

Dexamethasone 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 (e.g tuberculosis, typhoid, brucellosis; Only with simultaneous anti-infective therapy).
- Fetal lung maturation.
- Chemotherapy – associated nausea and vomiting.
- Multiple Myeloma – part of chemotherapy protocols (e.g VAD).
- Prevention and treatment of acute mountain sickness/HACE.

4.2. Posology and method of administration

Posology

Dexamethasone Rompharm contains 4 mg of dexamethasone phosphate 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 dexamethasone injection. These reactions, although they occur rarely in patients with a previous history of allergy to any drug, are most common.

Corticosteroids can mask some signs of infection or even induce the appearance of new infections or aggravate existing ones. Therefore, the use of Dexamethasone Rompharm is contraindicated, unless the patient receives adequate chemotherapy treatment and is subject to strict medical surveillance, in systemic fungal infections, disseminated tuberculosis, latent tuberculosis or with tuberculin reactivity, in patients with infestation or suspected digestive parasitic infestation, herpes, measles and chickenpox.

The administration of live virus vaccines, including smallpox, is contraindicated in people who are receiving immunosuppressive doses of corticosteroids. In the case of inactivated bacterial or viral vaccines, corticosteroids can prevent the immune response expected from vaccination (increase in serum antibodies). However, immunization procedures can be undertaken in patients who are receiving corticosteroids as replacement therapy, for example in Addison's disease.

Likewise, 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

Corticosteroids should be used with caution in patients with nonspecific 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 receiving high doses of corticosteroids, Signs of peritoneal irritation after gastrointestinal perforation may be minimal or absent. Fat embolism is a complication that can occur during hypercorticism.

In corticosteroid treatment, the lowest possible dose should always be used until the pathological situation is controlled; the subsequent dose reduction must be gradually, since their withdrawal can give rise to the appearance of symptoms such as fever, myalgia, arthralgia, malaise, etc., typical of the acute adrenocortical insufficiency of the withdrawal syndrome. This can occur even in patients without evidence of adrenal insufficiency.

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

Patients susceptible to infection with chickenpox 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 it can spread the infection if the germ causing it is not sensitive to the antibiotic used.

When given in high doses , taking antacids between meals can help prevent peptic ulcer disease.

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

Systemic corticosteroids should not be discontinued in patients who are already being treated with systemic (oral) corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease), but who do not require supplemental oxygen.

It should be noted that intramuscular administration has a slower level of absorption.

This medicinal product contains up to 14.5mmol (or 334 mg) sodium per maximum single dose of the medicinal product (350 mg dexamethasone 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. Patients at high risk for TLS, such as patients with high proliferation rate, high tumour burden, and high sensitivity to cytotoxic agents, should be closely monitored and appropriate precautions taken.

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

Children and the elderly

Chronic use of dexamethasone carries the risk of adrenal suppression and growth retardation, therefore, during its use in children, both body growth and development should be carefully evaluated.

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

Athletes
Athletes are informed that this medication can establish a positive analytical result in doping control.

Visual disturbances
Visual disturbances may occur with systemic and topical use of corticosteroids. If a patient experiences symptoms such as blurred vision or other visual disturbances, an ophthalmologist should be consulted to evaluate possible causes which may include cataracts, glaucoma or rare conditions such as central serous chorioretinopathy (CSCR) which have been reported following the use of systemic and topical corticosteroids.

Hypertrophic cardiomyopathy

Cases of hypertrophic cardiomyopathy have been reported after systemic administration of corticosteroids, including dexamethasone, to premature infants. In most reported cases, this effect was reversible after withdrawal of treatment. Preterm infants treated with systemic dexamethasone should undergo diagnostic evaluation and monitoring of cardiac structure and function (section 4.8).

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

Phenytoin, phenobarbital, adrenaline and rifampicin can increase the metabolic clearance of corticosteroids, causing a decrease in their blood levels and a decrease in their pharmacological activity, requiring an adjustment of the corticosteroid dose. These interactions can interfere with the dexamethasone suppression test, so the results obtained in these situations must be interpreted carefully during the administration of these drugs.

Dexamethasone can increase plasma levels of albendazole with possible inhibition of its effect, by inducing its hepatic metabolism.

Ephedrine may decrease plasma levels of dexamethasone, with possible loss of asthma control.

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

Due to its hypoprothrombin activity, acetylsalicylic acid should be used with caution during treatment with corticosteroids.

Prothrombin time should be checked frequently in patients receiving coumarin anticoagulants or indandione derivatives together with corticosteroids, since the latter alter the response of anticoagulants. Different studies have shown that they normally inhibit the response to coumarins, although there are some studies in which potentiation occurs.

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

Glucocorticoids can increase blood glucose concentration; it may be necessary to adjust the dosage of oral hypoglycemic agents or insulin or glucocorticoid when co-administered with any of these drugs.

Dexamethasone reduces the effects of antidiabetic drugs and potentiates the hypokalaemia of different diuretics and cardiotonic glycosides. The action of the corticosteroid is increased if combined with estrogens and decreased if used with aminoglutethimide, carbamazepine, phenytoin or rifampin. With indomethacin there is mutual potentiation of toxicity and with isoniazid a reduction in plasma levels of the latter.

Concomitant treatment with CYP3A inhibitors, including medicinal products containing cobicistat-, is expected to increase the risk of systemic adverse reactions. This combination should be avoided unless the benefit outweighs the increased risk of corticosteroid-related systemic adverse reactions, in which case patients should be followed for systemic corticosteroid reactions.

This medicine can alter the values in:
- Blood: increased cholesterol and glucose and decreased calcium, potassium and thyroid hormones.
- Urine: increased glucose.
- Skin tests: tuberculin and allergy patch tests.

4.6. Fertility, pregnancy and lactation

Pregnancy

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

Studies conducted with corticosteroids in experimental animals have shown congenital abnormalities (microcephaly, hepatomegaly, decreased size of the adrenal medulla and of the thymus), although some preliminary studies had suggested that the use of corticosteroids during pregnancy was associated with a 1% incidence of cleft palates in newborns, subsequent and better-constructed studies have not been able to establish this type of association. (See section 5.3)

In pregnant women, the benefit-risk ratio should be assessed, since the therapeutic benefit of this drug may eventually be greater than the potential teratogenic risk, and its use in pregnant women may be justified, under strict medical supervision, since there is a wide clinical casuistry that supports the use of corticosteroids during pregnancy, as long as they are therapeutically essential (hormone restoration treatments, etc.). Dexamethasone has been used in pre-term delivery (26-34 weeks) to improve the lung maturity of the newborn.

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

Studies have shown an increased risk of neonatal hypoglycemia following pre-natal administration of a short course of corticosteroids, including dexamethasone, to women at risk of late pre-term delivery.

Breast-feeding
Dexamethasone is excreted in breast milk and therefore prolonged treatment with high doses may affect the adrenal function of the nursing infant. It may also interfere with growth and endogenous corticosteroid production or cause other adverse effects in the nursing infant, and as a result monitoring of the infant is advised.

4.7. Effects on the ability to drive and use machines

No signs of impairment of the ability to drive and use machines that require special attention have been described.

4.8. Undesirable effects

In most cases, 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: decreased resistance to infection, oropharyngeal candidiasis.
Endocrine disorders: hyperglycaemia, adrenocortical insufficiency.
With high doses: signs of adrenal hyperactivity (Cushing's syndrome) with acneiform eruptions.
Metabolism and nutrition disorders: polyphagia.
Eye disorders: cataracts.
Vascular disorders: with high doses, flushing.
Gastrointestinal disorders: with high doses: gastric ulcer.
Skin and subcutaneous tissue disorders: delayed wound healing, local allergic reaction.
With 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 disorders, psychotic states.
Cardiac disorders: heart failure.
Vascular disorders: thromboembolism, edema, hypertension.
Skin and subcutaneous tissue disorders: sweating.
Musculoskeletal and connective tissue disorders: myasthenia
General disorders and administration site alterations: With rapid intravenous administration of high doses: allergic reactions and local injection site infection, generalised anaphylaxis, reddening of the face or cheeks, irregular heartbeat or palpitations, seizures.

Unknown frequency (cannot be estimated from the available data):

General disorders: hiccups.
Eye disorders: blurred vision (see also section 4.4.), chorioretinopathy.
Cardiac disorders: hypertrophic cardiomyopathy in premature babies (see section 4.4).

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

If the appearance of adverse reactions is observed, treatment should be discontinued and the pharmacovigilance systems notified.

Treatment should be discontinued immediately in the event that the patient experiences an episode of adrenal hyperactivity, for example: acne, hirsutism, skin hyperpigmentation, flushing 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:
https:// sideeffects.health.gov.il

4.9. Overdose

Acute intoxication or death by overdose can occur at a very low percentage. The symptoms that can be observed are anxiety, depression, mental confusion, spasms or gastrointestinal bleeding, hyperglycaemia, high blood pressure and edema. In these cases, the administration of phenobarbital is indicated, which reduces the half-life of dexamethasone by 44%, in addition to symptomatic and supportive treatment, which includes oxygen therapy, maintenance of body temperature, adequate fluid intake and control of electrolytes in serum and urine. The picture of gastrointestinal bleeding should be treated in a similar way to that of a peptic ulcer.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Dexamethasone Rompharm belongs to the therapeutic group H02AB02.

Dexamethasone is a fluorinated corticosteroid with a long duration of action, high anti-inflammatory and immunosuppressive potency and low mineralocorticoid activity.

Glucocorticoids cause profound and varied metabolic effects. They also modify immune response to various stimuli.

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

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

Glucocorticoids reduce the stability of certain RNA-messenger molecules, altering gene transcription. 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 produce hypothalamic-pituitary-adrenal (HPA) axis suppression through a negative feedback mechanism.

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

Glucocorticoids increase glucose availability through various actions that lead to increased hepatic glycogen stores, blood glucose concentrations, and insulin resistance.

Glucocorticoids increase lipolysis and mobilize fatty acids from adipose tissue, causing an increase in plasma fatty acid concentrations. They also decrease bone formation and increase bone resorption.

Dexamethasone, the active ingredient 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 corticosteroid with a long duration of action, since its effects are maintained for up to 72 hours, its total clearance varies between 2.8 and 3.5 mg/minute/kg, the 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 children under 2 years) and the biological half-life of 36-54 hours.

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

5.3. Preclinical safety data

Dexamethasone is a drug that acts on the hypothalamus-adreno-pituitary axis, so it can lead to Cushing's syndrome and osteoporosis, among others. However, this can occur after prolonged use of relatively high doses.

Although its teratogenic and embryotoxic effect has been detected in different animal species, there are no studies that allow these facts to be associated in humans. Dexamethasone has not been found 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

Revised in December 2022 according to MoHs guidelines