Diprospan® Injection

1. NAME OF THE MEDICINAL PRODUCT

Diprospan® Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betamethasone dipropionate 6.43 mg/ml (equivalent to 5 mg of betamethasone) and betamethasone sodium phosphate 2.63 mg/ml (equivalent to 2 mg of betamethasone).

Excipients with known effect:
This medicinal product contains 9 mg of benzyl alcohol per mL.
Diprospan contains (methyl parahydroxybenzoate) and Diprospan contains (propyl parahydroxybenzoate).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for injection
Diprospan suspension for injection is a clear, colourless, slightly viscous liquid containing easily re-suspendable white to off-white particles, free from foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIPROSPAN Sterile Aqueous Suspension is indicated for the treatment of acute and chronic corticosteroid-responsive disorders such as the following conditions:

Musculoskeletal and Soft Tissue Conditions:

Rheumatoid arthritis, osteoarthritis, bursitis, ankylosing spondylitis, epicondylitis, radiculitis, coccydynia, torticollis, sciatica, lumbago, ganglion cyst, exostosis, fasciitis.

Allergic Conditions:

Chronic bronchial asthma (including adjunctive therapy for status asthmaticus), hay fever, angioneurotic edema, allergic bronchitis, seasonal or perennial allergic rhinitis, drug reactions, serum sickness, insect bites.

Dermatologic Conditions:

Atopic dermatitis (nummular eczema), neurodermatitis (circumscribed lichen simplex), necrobiosis lipoidica diabeticorum, alopecia areata, discoid lupus erythematosus, psoriasis, keloids, pemphigus, dermatitis herpetiformis, urticaria, hypertrophic lichen planus, contact dermatitis, severe solar dermatitis, cystic acne.

Collagen Diseases:

Disseminated lupus erythematosus, scleroderma, dermatomyositis, polyarteritis nodosa.

Neoplastic Diseases:

For palliative management of leukemias and lymphomas in adults; acute leukemia of childhood.

Other Conditions:

Adrenogenital syndrome, ulcerative colitis, regional ileitis, sprue, podiatric conditions (bursitis under heloma durum [corn], hallux rigidus, digiti quinti varus [fifth toe varus]), disorders requiring subconjunctival injection, corticosteroid-responsive blood dyscrasias, nephritis and nephrotic syndrome. Primary or secondary adrenocortical insufficiency may be treated with Diprospan Sterile Aqueous Suspension but should be supplemented with mineralocorticoids.

Diprospan Sterile Aqueous Suspension is recommended for (1) intramuscular injection in conditions responsive to systemic corticosteroids; (2) injection directly into the affected soft tissues where indicated; (3) intra-articular and peri-articular injection in arthritis; (4) intralesional injection in various dermatologic conditions; (5) local injection in certain inflammatory and cystic disorders of the foot and soft tissue.

4.2 Posology and method of administration

DOSING REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE SPECIFIC DISEASE, THE SEVERITY OF THE CONDITION AND THE RESPONSE OF THE PATIENT.

The initial dose should be maintained or adjusted until a satisfactory response is observed. If a satisfactory clinical response does not occur after a reasonable period of time, treatment with Diprospan Suspension should be discontinued and other appropriate therapy initiated.

Systemic Administration:

For systemic therapy, treatment is initiated with 1 to 2 ml in most conditions and repeated as necessary. Administration is by deep intramuscular (IM) injection in the gluteal region. Dosage and frequency of administration will depend on the severity of the patient's condition and the therapeutic response.

In a severe illness, such as lupus erythematosus or status asthmaticus which has been resolved by appropriate life-saving procedures, 2 ml might be required initially.

A wide variety of dermatologic conditions respond to IM injections of corticosteroids. An IM injection of 1 ml, repeated according to the response of the condition, has been found to be effective.

In respiratory tract disorders, onset of relief of symptoms has occurred within a few hours after IM injection of Diprospan Suspension. Effective control of symptoms with 1 to 2 ml is obtained in bronchial asthma, hay fever, allergic bronchitis and allergic rhinitis.

In the treatment of acute or chronic bursitis, excellent results are obtained with 1 to 2 ml IM injection of Diprospan Suspension, repeated as necessary.

Local Administration:

Concomitant use of local anesthetic is rarely necessary. If coadministration of a local anesthetic is desired, Diprospan Suspension may be mixed (in the syringe) with 1% or 2% procaine hydrochloride or lidocaine, using formulations which do not contain parabens. Similar local anesthetics may also be used. Anesthetics containing methylparaben, propylparaben, phenol, etc. should be avoided. The required dose of Diprospan Suspension is first withdrawn into the syringe. The local anesthetic is then drawn in, and the syringe is shaken briefly.

In acute subdeltoid, subacromial, olecranon, and prepatellar bursitis, an intrabursal injection of 1 to 2 ml of Diprospan Suspension may relieve pain and restore full range of movement within a few hours. Chronic bursitis may be treated with reduced dosage once acute symptoms are controlled. In acute tenosynovitis, tendinitis, and peritendinitis, one injection of Diprospan Suspension should alleviate the condition. In chronic forms of these conditions, it may be necessary to repeat the injections as the patient's condition requires.

Following 0.5 to 2 ml intra-articular administration of Diprospan Suspension, relief of pain, soreness, and stiffness associated with rheumatoid arthritis and osteoarthritis may be experienced within two to four

hours. Duration of relief, which varies widely in both diseases, is four or more weeks in the majority of cases. An intra-articular injection of Diprospan Suspension is well tolerated in the joint and peri-articular tissues. Recommended doses for intra-articular injection are: large joints (knee, hip, shoulder), 1 – 2 ml; medium joints (elbow, wrist, ankle), 0.5 – 1 ml; small joints (foot, hand, chest), 0.25 – 0.5 ml.

Dermatologic conditions may respond to intralesional administration of Diprospan Suspension. An intradermal dosage of 0.2 ml/cm^2 of Diprospan Suspension evenly injected with a tuberculin syringe and a 26-gauge needle is recommended. The total amount of Diprospan Suspension injected at all sites each week should not exceed 1 ml.

Diprospan Suspension may be used effectively in disorders of the foot that are responsive to corticosteroids.

Bursitis under heloma durum (corn) may be controlled with two successive injections of 0.25 ml each. In some conditions such as hallux rigidus, digiti quinti varus (fifth toe varus) and acute gouty arthritis, onset of relief may be rapid. A tuberculin syringe with a 25-gauge needle is suitable for most injections. Recommended doses at intervals of approximately one week: bursitis under heloma (corn) durum or molle, 0.25 – 0.5 ml; bursitis under calcaneal spur, 0.5 ml; bursitis over hallux rigidus, 0.5 ml; bursitis over digiti quinti varus (fifth toe varus), 0.5 ml; synovial cyst, 0.25 – 0.5 ml; Morton's neuralgia (metatarsalgia), 0.25 – 0.5 ml; tenosynovitis, 0.5 ml; periostitis of cuboid, 0.5 ml; acute gouty arthritis, 0.5 – 1 ml. After a favorable response is obtained, the proper maintenance dosage should be determined by decreasing the initial dose in small decrements at appropriate time intervals until the lowest dose which will maintain an adequate clinical response is determined.

Exposure of the patient to stressful situations unrelated to the existing disease may necessitate an increased dose of Diprospan Suspension. If the drug is to be discontinued after long-term therapy, the dose should be decreased gradually.

Shake before use.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Hypersensitivity to corticosteroids;
- Systemic fungal infections.

In patients with idiopathic thrombocytopenic purpura, Diprospan CANNOT be administered intramuscularly.

4.4 Special warnings and precautions for use

Diprospan cannot be used for intravenous or subcutaneous administration.
Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

ANTISEPTIC TECHNIQUES ARE NECESSARY.

Diprospan contains two betamethasone esters, one of which, betamethasone sodium phosphate, disappears rapidly from the injection site. Therefore, when using this product, the physician must take into account that this soluble portion of Diprospan may have a systemic effect.

Eliminating or abruptly reducing administration during chronic use (at very high doses, after only a short time), or when an increase in corticosteroid requirements (following stress: infection, trauma, surgery)

may precipitate adrenal insufficiency. It is therefore necessary to reduce the dose gradually. In stressful situations, it is sometimes necessary to administer corticosteroids again or to increase the dose.

The dose reduction should be achieved under close medical supervision and it is sometimes necessary to monitor the patient for up to 1 year after cessation of prolonged or high-dose treatment.

The symptoms of adrenal insufficiency are: discomfort, muscle weakness, mental disorders, lethargy, muscle and bone pain, desquamation of the skin, dyspnea, anorexia, nausea, vomiting, fever, hypoglycemia, hypotension, dehydration, and even death following abrupt discontinuation of the treatment. Treatment of adrenal insufficiency consists in administering corticosteroids, mineralocorticoids, water, sodium chloride and glucose.

Rapid intravenous injection of high doses of corticosteroids can cause cardiovascular collapse; this is why the injection has to be administered over a 10-minute period.

Rare instances of anaphylactoid/anaphylactic reactions with a possibility of shock have occurred in patients receiving parenteral corticosteroid therapy. Appropriate precautionary measures should be taken with patients who have a history of allergic reactions to corticosteroids.

During prolonged corticosteroid therapy, consider switching from parenteral to oral administration after weighing the potential benefits and risks.

For intra-articular injections, it is important to know that:
- This type of administration can have local and systemic effects.
- It is essential to examine any liquid that may be present in the joint, in order to exclude a septic process.
- Avoid local injection into a previously infected joint.
- A net increase in pain and local swelling, further decrease in joint mobility, fever and discomfort should raise the question of septic arthritis. If the diagnosis of infection is confirmed, appropriate antimicrobial treatment must be initiated.
- Do not inject corticosteroids in unstable joints, infected areas or intervertebral spaces.
- Repeated injections into osteoarthritis-affected joints can aggravate the destruction of the joint.
- Avoid injecting corticosteroids directly into tendons because tendon rupture may occur subsequently.

Intramuscular injection of corticosteroids should be performed deep in large muscle masses to avoid local tissue atrophy.

The administration of a corticosteroid in soft tissue, or intralesional and intra-articular administration, can induce systemic and local effects.

Specific groups at risk
In diabetics, betamethasone may be used only for a short period and only under close medical supervision, given its glucocorticoid properties (transformation of glucose into proteins).

There is an increase in the glucocorticoid effect in patients with hypothyroidism or cirrhosis.

The use of Diprospan in ocular herpes simplex should be avoided, given the possibility of perforation of the cornea.

Psychotic disorders can occur during treatment with corticosteroids. Predisposition to emotional instability or psychosis may worsen during treatment with corticosteroids.

Caution is advised in case of:
- nonspecific ulcerative colitis, impending perforation, abscess and other pyogenic infections;
- diverticulitis;
- intestinal anastomosis;
- gastroduodenal ulcer;
- renal insufficiency;
- hypertension;
- osteoporosis;
- myasthenia gravis;

- glaucoma;
- acute psychoses;
- viral and bacterial infections;
- growth retardation;
- tuberculosis;
- Cushing's syndrome;
- diabetes;
- heart failure;
- difficult-to-treat epilepsy;
- thromboembolism or thrombophlebitis tendencies;
- pregnancy.

Since the complications of corticosteroid treatment depend on the dose and duration of treatment, the risk/benefit ratio for each patient regarding the dose and duration of treatment needs to be considered.

Corticosteroids may mask certain signs of infection or make the detection of infection more difficult. Due to a decrease in resistance, new infections can occur during use.

Prolonged use can lead to a posterior subcapsular cataract (especially in children) or to glaucoma, which can damage the optic nerves and may exacerbate secondary ocular infections due to fungi or viruses.
In case of prolonged treatment (over 6 weeks), it is necessary to undergo regular ophthalmological examinations.
Average and large doses of corticosteroids can induce hypertension, fluid retention and increased potassium excretion. These effects are less likely to occur with the synthetic derivatives, except when used at high doses. A low sodium diet and potassium supplements may be considered. All corticosteroids increase calcium excretion.

PATIENTS ON CORTICOTHERAPY CANNOT RECEIVE THE FOLLOWING TREATMENTS:
- SMALLPOX VACCINATION.
- OTHER METHODS OF IMMUNIZATION (ESPECIALLY AT HIGH DOSE) BECAUSE OF THE RISK OF NEUROLOGICAL COMPLICATIONS AND INADEQUATE ANTIBODY RESPONSE.

However, patients receiving corticosteroids as replacement therapy may be immunized (e.g., Addison's disease).
Patients, especially children, receiving immunosuppressive doses of corticosteroids should be warned to avoid exposure to chickenpox or measles.

In case of active tuberculosis, corticosteroids should be limited to cases of fulminating or disseminated tuberculosis, in which corticosteroids are used in combination with a suitable anti-tubercular treatment regimen.

If corticosteroids are indicated in patients with latent tuberculosis or reacting to tuberculin, strict monitoring is necessary because disease reactivation can occur. During prolonged corticosteroid therapy, patients should receive chemoprophylaxis.

If using rifampicin in a chemoprophylaxis program, its enhancing effect on the metabolic hepatic clearance of corticosteroids must be remembered; it may be necessary to adjust the dose of the corticosteroid.

As corticosteroids can disturb the growth of infants and children and inhibit the endogenous production of corticosteroids, it is important to monitor their growth and development carefully in the event of prolonged treatment.

Corticosteroids may sometimes alter the motility and number of spermatozoa in some patients.

Diprospan contains benzyl alcohol.
Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Do not administer to premature babies or newborns at term (up to 4 weeks). Do not administer for more than a week in young children (less than 3 years old).

Large amounts of benzyl alcohol may cause metabolic acidosis. Special precautions should be taken when prescribing Diprospan to neonates, pregnant or breast-feeding patients and patients with liver or kidney disease.

Diprospan contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium-free'.

Diprospan contains (methyl parahydroxybenzoate) and (propyl parahydroxybenzoate)
which may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm.

Visual disturbance

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) 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 of visual disturbances 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

Interaction with other medicinal products:
Combination with phenobarbital, rifampin, phenytoin or ephedrine may enhance the metabolism of corticosteroids, resulting in a decrease in therapeutic effect.

PATIENTS ON CORTICOTHERAPY CANNOT RECEIVE THE FOLLOWING TYPES OF TREATMENT:
- SMALLPOX VACCINATION.
- OTHER METHODS OF IMMUNIZATION (ESPECIALLY AT HIGH DOSE) BECAUSE OF THE RISK OF NEUROLOGICAL COMPLICATIONS AND INADEQUATE ANTIBODY RESPONSE.

However, patients receiving corticosteroids as replacement therapy may be immunized (e.g., Addison's disease).

The combination with diuretics such as thiazides may increase the risk of glucose intolerance.

Patients simultaneously receiving a corticosteroid and an estrogen must be monitored for excessive corticosteroid effects.

The simultaneous administration of corticosteroids and cardiac glycosides may increase the risk of arrhythmias or digitalis toxicity related to hypokalemia. Often, patients using cardiac glycosides also take diuretics which induce potassium depletion; in this case, it is essential to conduct potassium level determinations. Corticosteroids may worsen the potassium depletion caused by amphotericin B. In all patients taking one of these medication combinations, serum electrolytes, particularly serum potassium, should be closely monitored.

The simultaneous use of corticosteroids and coumarin-type anticoagulants may increase or decrease the anticoagulant effects, which may require a dosage adjustment. In patients taking anticoagulants in combination with glucocorticoids, the possibility of gastrointestinal ulceration induced by corticosteroids, or increased risk of internal bleeding, must be considered.

Corticosteroids may decrease the concentration of salicylates in the blood. When lowering the dose of corticosteroids or discontinuing treatment, patients should be checked for the presence of salicylism. The combination of glucocorticoids with salicylates may increase the frequency and severity of a gastrointestinal ulcer.

The combination with non-steroidal anti-inflammatories or alcohol can lead to an increased risk of developing a gastrointestinal ulcer or the worsening of an existing ulcer.

In diabetics, it is sometimes necessary to adjust the dose of oral antidiabetic agents or insulin, given the intrinsic hyperglycemic effect of glucocorticoids.

Combination with somatropin may inhibit the response to this hormone. Betamethasone doses greater than 300-450 µg (0.3 to 0.45 mg) per m^2 of body surface area per day should be avoided during administration of somatotropin.

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.

Other forms of interactions:
Laboratory tests
Corticosteroids may influence the nitro blue tetrazolium reduction test and produce false negative results.

When the patient is treated with corticosteroids, this fact should be taken into account when interpreting the parameters and laboratory tests (skin tests, thyroid hormone levels, etc.).

4.6 Fertility, pregnancy and lactation

Given the lack of adequate teratogenic studies in humans, glucocorticoids can only be administered during pregnancy, breast-feeding and in women of fertile age after having thoroughly evaluated the health benefits and potential risks of these medications for the mother, the embryo or the fetus.

Pregnancy

When prenatal corticotherapy is indicated, the advantages and disadvantages need to be weighed and the clinical benefit compared to the side effects (including the inhibition of growth and the increased risk of infection).

In some cases it is necessary to continue the corticosteroid treatment during pregnancy or even increase the dose (e.g., in replacement corticotherapy).

Intramuscular administration of betamethasone induces a significant decrease in the frequency of dyspnea in the fetus when the product is administered more than 24 hours before delivery (before the 32^{nd} week of gestation).

Published data show that the prophylactic use of corticosteroids after the 32^{nd} week of pregnancy is still controversial. Therefore, the physician should weigh the benefits and potential risks for the mother and fetus when using corticosteroids after the 32^{nd} week of pregnancy.

Corticosteroids are not indicated to treat hyaline membrane disease after birth.

In prophylactic treatment of hyaline membrane disease in premature infants, do not administer corticosteroids to pregnant women with preeclampsia or eclampsia or with signs of placental lesions.

Children born to mothers given high doses of corticosteroids during pregnancy should be carefully monitored to detect any signs of adrenal insufficiency.

When betamethasone injections have been administered to mothers before birth, infants show a transient inhibition of fetal growth hormone and presumably of the pituitary hormones that regulate the production of steroids, both in the definitive zones and fetal zones of the fetal adrenals. However, inhibition of fetal hydrocortisone has not interfered with the pituitary-adrenal responses to stress after birth.

As corticosteroids readily cross the placenta, newborns and infants born to mothers who received corticosteroids during most or part of their pregnancy should be subject to careful examination in order to detect a possible, though very rare, congenital cataract.

Women who received corticosteroids during pregnancy should be monitored during and after contractions and during childbirth to detect adrenal insufficiency due to the stress caused by birth.

Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of betamethasone to women at risk for late preterm delivery.

Breastfeeding
Corticosteroids cross the placental barrier and are excreted in breast milk.

Given that Diprospan may induce adverse reactions in breast-fed infants, a decision must be made whether to stop breast-feeding or stop the medicinal product, taking into account the importance of the medicinal product for the mother.

4.7 Effects on ability to drive and use machines

Caution should be exercised concerning the central effects when administered at high doses (euphoria, insomnia) and with regard to the vision disorders that can occur with prolonged treatment.

4.8 Undesirable effects

The adverse reactions observed with Diprospan, which are the same as those mentioned for other corticosteroids, are related to both dose and duration of treatment.

Among the adverse reactions to corticosteroids in general, the following effects are to be particularly noted:

Fluid and electrolyte disorders:
Sodium retention - Potassium loss - Hypokalemic alkalosis - Fluid retention - Congestive heart failure in susceptible patients - Hypertension;

Musculoskeletal disorders:
Muscular weakness - Loss of muscle mass - Aggravation of myasthenic symptoms in myasthenia gravis - Osteoporosis with sometimes severe bone pain and spontaneous fractures (vertebral compression fractures) - Aseptic bone necrosis (femoral and humeral head) - Tendon rupture - Steroid myopathy - Pathological fractures - Joint instability;

Skin disorders:
Skin atrophy - Delayed healing - Thin and fragile skin - Petechiae - Bruising - Allergic dermatitis - Angioneurotic edema - Facial erythema - Increased sweating - Urticaria;

Digestive disorders:
Gastric ulcer with bleeding and possible perforation - Pancreatitis - Abdominal distension - Intestinal perforation - Ulcerative esophagitis - Nausea - Vomiting;

Neurological disorders:
Seizures - Vertigo - Headache - Migraines - Increased intracranial pressure (pseudotumor cerebri);

Psychiatric disorders:
Euphoria - Mood Disorders - Personality changes and severe depression - Hyperirritability - Insomnia - Psychotic reactions especially in patients with a psychiatric history - Depression;

Ophthalmic disorders:
Increased intraocular pressure (pseudotumor cerebri: see neurological); Glaucoma - Posterior subcapsular cataract - Exophthalmos - Vision blurred (see also section 4.4).

Endocrine disorders:
Clinical symptoms of Cushing's syndrome - Menstrual disorders - Increased need for insulin or oral antidiabetic agents in diabetics - Inhibition of fetal child growth - Reduced tolerance to carbohydrates - Signs of latent diabetes mellitus - Secondary inhibition of the pituitary and the adrenal cortex, especially harmful in case of stress (such as trauma, surgery and disease);

Metabolic disorders:
Negative nitrogen balance with protein degradation - Lipomatosis - Weight gain;

Immunity disorders:
Corticosteroids can cause an inhibition of skin tests, mask the symptoms of infection and active a latent infection. They can also decrease resistance to infection, especially when due to mycobacteria, tuberculosis, Candida albicans or viruses.

Other:
Anaphylactic or allergic reactions, hypotensive reactions or reactions related to shock.

THE FOLLOWING ADVERSE REACTIONS MAY BE OBSERVED DURING PARENTERAL CORTICOTHERAPY:
Rare cases of blindness associated with intralesional treatment of the face and head - Hyperpigmentation or hypopigmentation - Subcutaneous and cutaneous atrophy - Sterile abscess - Post-injection exacerbation (after intra-articular use) - Charcot arthropathy.

After repeated intra-articular administration, joint damage may occur. There is a risk of contamination.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
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

Symptoms:
Acute overdosage of glucocorticoids, including betamethasone, is not life-threatening.

Except in extreme doses, it is unlikely that a few days of glucocorticoid overdose will have negative consequences in the absence of specific contraindications such as diabetes, glaucoma, active peptic ulcer, or when administering medications such as digitalis, coumarin anticoagulants or potassium-sparing diuretics.

Measures:
The complications resulting from the metabolic effects of corticosteroids, or the deleterious effects of the main disease or concomitant diseases, as well as the complications resulting from medication interactions, must be treated appropriately. It is necessary to ensure adequate fluid intake and monitor electrolytes in the serum and urine, paying particular attention to the sodium and potassium balance. If necessary, any electrolyte imbalance must be treated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, glucocorticoids, ATC code: H02A B01.

Betamethasone is a synthetic glucocorticoid (9 alpha-fluoro-16 beta-methylprednisolone).
Betamethasone has strong anti-inflammatory, immunosuppressive and anti-allergic activity.

Betamethasone has no clinically significant mineralocorticoid effect. Glucocorticoids diffuse across cell membranes and form complexes with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin) and stimulate the transcription of messenger RNA and the protein synthesis of various enzymes. These are finally responsible for the effects observed in systemic glucocorticoid use. In addition to their significant effect on the inflammatory and immune processes, glucocorticoids also influence the metabolism of carbohydrates, proteins and lipids. Finally, they also have an effect on the cardiovascular system, skeletal muscles and the central nervous system.

Effect on inflammatory and immune processes:
The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for a very substantial part of their therapeutic applications. The main aspects of these properties are: reduction in the number of immuno-active cells at the inflammatory site, reduced vasodilation, stabilization of lysosomal membranes, inhibition of phagocytosis, reduced production of prostaglandins and related substances.

The anti-inflammatory activity is about 25 times greater than that of hydrocortisone, and 8 to 10 times greater than that of prednisolone (on a weight basis).

Effect on the metabolism of carbohydrates and proteins:
Glucocorticoids stimulate protein catabolism. In the liver, the released amino acids are converted into glucose and glycogen by the process of gluconeogenesis. Glucose uptake in peripheral tissues decreases, which leads to hyperglycemia and glucosuria, especially in patients with a diabetic predisposition.

Effect on lipid metabolism:
Glucocorticoids have lipolytic activity. This lipolysis is more pronounced in the limbs. Glucocorticoids also have a lipogenic effect that occurs mainly in the trunk, neck and head. As a whole, these effects lead to a redistribution of fat deposits.

The maximum pharmacological activity of corticosteroids appears later than the peak serum levels, suggesting that most effects of these medications are not based on direct activity of the medicinal product, but on the modification of enzyme activity.

5.2 Pharmacokinetic properties

Betamethasone sodium phosphate and betamethasone dipropionate are resorbed from the injection site and induce therapeutic effects and other pharmacological effects, both locally and systemically.

Betamethasone sodium phosphate is highly soluble in water and is metabolized in the body into betamethasone, the biologically active steroid. 2.63 mg of betamethasone sodium phosphate is equivalent to 2 mg of betamethasone.

Prolonged activity is obtained using betamethasone dipropionate. This practically insoluble product constitutes a deposit, so that it is less rapidly resorbed and relieves symptoms longer.

Blood levels	***Intramuscular injection***	
	Betamethasone	
	natrii phosphas	***Dipropionas***
Maximum plasma concentration	1 hour after administration	Slow absorption
Plasma half-life after a single dose	from 3 to 5 hours	Progressive metabolism
Excretion	24 hours	More than 10 days
Biological half-life	36 to 54 hours	

Betamethasone is metabolized in the liver. Betamethasone binds primarily to albumin. In patients with a liver disorder, its clearance is slower or delayed.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogols, benzyl alcohol, sodium chloride, sodium carboxymethylcellulose, disodium hydrogen phosphate dihydrate, methyl parahydroxybenzoate, polysorbate 80, propyl parahydroxybenzoate , disodium edetate, hydrochlorid acid, nitrogen, water for injections.

6.2 Incompatibilities

The concomitant use of a local anesthetic is rarely necessary. If coadministration of a local anesthetic is desired, Diprospan can be mixed (in the syringe, not in the ampoule), with lidocaine hydrochloride (1% or 2%), with procaine hydrochloride (1% or 2%) or with a similar local anesthetic, using formulations that do not contain parabens. Avoid the use of anesthetics containing methylparaben, propylparaben, phenol, etc.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store between 2°C-25°C. Do not freeze.

6.5 Nature and contents of container

Diprospan Ampoule:
Boxes of 1 ampoule of 1 ml
Boxes of 1 ampoule of 2 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MANUFACTURER

Organon LLC, NJ USA

8. LICENSE HOLDER AND ADDRESS

Organon Pharma Israel Ltd., 1 Atir Yeda, Kfar Saba

9. MARKETING AUTHORIZATION NUMBER

047-07-24139

Revised in March 2022 according to MOH guidelines.