
1. NAME OF THE MEDICINAL PRODUCT

Flosteron suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension for injection (1 ampoule) contains 2 mg betamethasone as disodium phosphate and 5 mg betamethasone as dipropionate.

Excipients with known effect:
Benzyl alcohol, propyl parahydroxybenzoate, methyl parahydroxybenzoate, sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection: white suspension, free from particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Corticosteroid hormone therapy is an adjunct to, and not a replacement for, conventional therapy.
Intramuscular administration
Flosteron is indicated for the treatment of various rheumatic, dermatological, allergic diseases, disorders of the collagen and other tissues, known for their response to treatment with corticosteroids.
Musculoskeletal administration (intra-articular and periarticular administration and direct administration into the soft tissues)
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in osteoarthritis, rheumatoid polyarthritis.
Intralesional administration
In various dermatologic conditions.
Local administration in the tissue of the foot
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in bursitis under heloma durum, bursitis under plantar callosity, bursitis under calcaneal spur, bursitis over hallux rigidus or digiti quinti varus, synovial cyst, Morton's neuralgia (metatarsalgia), tenosynovitis, periostitis of cuboid.
Typical situations
Allergic conditions
Status asthmaticus, chronic bronchial asthma, seasonal or perennial allergic rhinitis, severe allergic bronchitis, contact dermatitis, atopic dermatitis, hay fever, angioneurotic edema, serum sickness, hypersensitivity reactions to medications or insect bites.
Rheumatic diseases
Osteoarthritis, rheumatoid arthritis, bursitis, lumbago, sciatica, coccydynia, acute gouty arthritis, torticollis, ganglion cyst, ankylosing spondylitis, radiculitis, exostosis, fasciitis.
Dermatologic diseases
Atopic dermatitis (nummular eczema), neurodermatitis (circumscribed lichen simplex), contact dermatitis, severe solar dermatitis, urticaria, hypertrophic lichen planus, necrobiosis lipoidica diabeticorum, alopecia areata, discoid lupus erythematosus, psoriasis, keloids, pemphigus, dermatitis herpetiformis and cystic acne.
Collagen diseases
During an exacerbation or as maintenance therapy in selected cases of disseminated lupus erythematosus, polyarteritis nodosa, scleroderma and dermatomyositis.
Neoplastic diseases
Palliative management of leukemias and lymphomas in adults and acute leukemia of childhood.
Other conditions

Adrenogenital syndrome, ulcerative colitis, regional ileitis, sprue, corticosteroid-responsive blood dyscrasias, nephritis and nephrotic syndrome.
Primary or secondary adrenocortical insufficiency may be treated with Flosteron but should be supplemented with mineralocorticoids, if applicable.

4.2. Posology and method of administration

Shake well before using.
Dosing requirements are variable and must be individualized on the basis of the specific disease, the severity of the disease and the response of the patient.
The dose should be minimal and the period of administration should be as much as possible short.
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 Flosteron should be discontinued through gradual dose reduction and other appropriate therapy initiated.
After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached.
Flosteron is not for intravenous or subcutaneous use.
Systemic therapy
For systemic therapy, treatment is initiated with 1-2 mL in most conditions and repeated as necessary. Administration is by deep 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 Flosteron. 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 Flosteron. 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 Flosteron, repeated as necessary.
Local administration
Flosteron can be mixed with a local anesthetic in the same syringe, if necessary.
In acute subdeltoid, subacromial, olecranon, and prepatellar bursitis, an intrabursal injection of 1 to 2 ml of Flosteron 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 tendinitis, tenosynovitis, and peritendinitis, one injection of Flosteron 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 Flosteron, 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 Flosteron is well tolerated in the joint and periarticular tissues.
Recommended doses for intra-articular injection are:
- large joints (e.g., knee, hip): 1 – 2 ml;
- medium joints (e.g., elbow): 0.5 – 1 ml;
- small joints (e.g., hand): 0.25 – 0.5 ml.

Dermatologic conditions may respond to intralesional administration of Flosteron. Response of some lesions not treated directly may be due to a slight systemic effect of the drug.
An intradermal dosage (not subcutaneously) of 0.2 ml/cm^2 of Flosteron evenly injected with a tuberculin syringe and a 26-gauge needle is recommended. The total amount of Flosteron injected at all sites each week should not exceed 1 ml.
Flosteron may be used effectively in disorders of the foot that are responsive to corticosteroids.

Bursitis under heloma durum may be controlled with two successive injections of 0.25 ml each. In some conditions such as hallux rigidus, digiti quinti varus and acute gouty arthritis, onset of relief may be rapid. A tuberculin syringe with a 25-gauge, 1.9 cm needle is suitable for most injections into the foot.
Recommended doses at intervals of approximately one week:
Bursitis:

- under a corn	0.25–0.5 mL
- under calcaneal spur	0.5 mL
- over hallux rigidus	0.5 mL
- over digiti quinti varus	0.5 mL
Synovial cyst	0.25–0.5 mL
Morton's neuralgia (metatarsalgia)	Morton's neuralgia (metatarsalgia) 0.25–0.5 mL
Tenosynovitis	Tenosynovitis 0.5 mL
Periostitis of cuboid	Periostitis of cuboid 0.5 mL
Acute gouty arthritis	Acute gouty arthritis 0.5–1 mL

4.3. Contraindications

Hypersensitivity to any of the active substances or excipients, or corticosteroids *(see section 6.1 List of excipients)*.
Patients with systemic fungal infections.
In patients with idiopathic thrombocytopenic purpura, Flosteron CANNOT be administered intramuscularly.

4.4. Special warnings and special precautions for use

Flosteron is not for intravenous or subcutaneous use.
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.
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.
Strict aseptic technique is mandatory in its use.
Flosteron contains 2 betamethasone esters, one of which, betamethasone sodium phosphate, disappears rapidly from the injection site. The potential for systemic effect produced by this soluble portion of Flosteron should therefore be taken into account by the physician when using this preparation.
Following cessation or too rapid reduction dose of the preparation after long-term use (in the case of very high doses already after a short period), or at an increased need for corticosteroids (exposure of the patient to stress, e.g., serious infection, surgery or injury) adrenocortical insufficiency may occur. Therefore the dose should be decreased gradually. In any situation of stress it may be necessary to reinstitute corticosteroid therapy or if the patient is receiving corticosteroids already, dosage may have to be increased.
Dose reduction should be carried out under the close supervision of a physician. In addition it is sometimes necessary to monitor the patient for a period up to one year following cessation of long-term or high-dose Flosteron therapy.
Symptoms of adrenocortical insufficiency include malaise, muscle weakness, mental disorders, lethargy, muscle and bone pain, peeling skin, dyspnea, anorexia, nausea, vomiting, fever, hypoglycemia, hypotension, dehydration, death due to abrupt discontinuation of treatment. The treatment of adrenocortical insufficiency consists of the administration of corticosteroids, mineralocorticoids, water, sodium chloride and glucose.

With long-term corticosteroid therapy, transfer from parenteral to oral administration should be considered after weighing the potential benefits and risks.
For intra-articular injection, it is important to know the following:

- Intra-articular administration may produce systemic as well as local effects.
- Examination of any joint fluid present is necessary to exclude a septic process.
- Local injection into previously infected joint is to be avoided.
- An increase in pain and local swelling, further restriction of joint motion, fever and malaise are suggestive of septic arthritis. If the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.
- Corticosteroids should not be injected into unstable joints, infected areas or intervertebral spaces.
- Repeated injections into joints of osteoarthritis may increase joint destruction.
- Avoid injecting corticosteroids directly into the substance of tendons because delayed appearance of tendon rupture has resulted.

Intramuscular injection of corticosteroids should be given deep into large muscle masses to avoid local tissue atrophy.
Soft tissue, intralesional and intra-articular administration of a corticosteroid may produce local and systemic as well as effects.
Specific risk groups
Taking into account the properties of glucocorticoids (the transformation of protein to glucose) in diabetic patients, betamethasone may be used only for a short period of time and under constant medical supervision.
Corticosteroid effect is enhanced in patients with hypothyroidism or in those with cirrhosis.
It is necessary to avoid the use of Flosteron in patients with ocular herpes simplex because of possible corneal perforation.
Psychic derangements may appear with corticosteroid therapy. Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.
Corticosteroids should be used with caution in the following cases: nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections; diverticulitis; intestinal anastomoses; peptic ulcer; renal failure; hypertension; osteoporosis; myasthenia gravis; glaucoma; acute psychosis; viral and bacterial infections; growth retardation; tuberculosis; Cushing syndrome; diabetes; heart failure; epilepsy difficult to treat; tendency to thromboembolia or thrombophlebitis; pregnancy.
Since complications of corticosteroid therapy are dependent on the dose and duration of treatment, should take into account of the risk/benefit ratio for each patient, with respect to the dose and duration of treatment.
Corticosteroids can mask signs of infection or complicate its detection. Due to a decrease in resistance, new infections may occur during use of the drug.
Prolonged use of the drug may produce posterior subcapsular cataracts (especially in children) or glaucoma with possible damage to the optic nerves and may enhance secondary ocular infections due to fungi or viruses.
Periodic ophthalmologic examinations are recommended, particularly in patients receiving the drug for more than 6 months.
Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be considered. All corticosteroids increase calcium excretion.
The following treatments are contraindicated in patients receiving corticosteroid therapy:
- vaccination against smallpox;
- other immunization procedures should not be undertaken in patients receiving corticosteroids (especially high doses), because of possible hazards of neurological complications and lack of antibody response.

However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison disease).
Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. This is of particular importance in children.
Corticosteroid therapy in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for management in conjunction with an appropriate antituberculous regimen.
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy, patients should receive chemoprophylaxis.
If rifampin is used in a chemoprophylactic program, its enhancing effect on metabolic hepatic clearance of corticosteroids should be considered; adjustment in corticosteroid dosage may be required.
Since corticosteroid administration can disturb growth rates and inhibit endogenous corticosteroid production in infants and children, the growth and development of these patients receiving prolonged therapy should be followed carefully.
Corticosteroid therapy may alter the motility and number of spermatozoa.
Flosteron contains benzyl alcohol, which may cause toxic and anaphylactoid reactions in infants and children up to 3 years. The drug should not be administered to premature babies or newborns at term.
Flosteron contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (sometimes delayed type), and in exceptional cases – difficulty in breathing.
Flosteron contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
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

Drug interactions
Corticosteroids (including betamethasone) are metabolized by CYP3A4.
Concurrent use of phenobarbital, rifampin, phenytoin or ephedrine may enhance the metabolism of corticosteroids, reducing their therapeutic effects.
Co-treatment with CYP3A inhibitors, (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir, cobicistat-containing products) may lead to increased exposures of corticosteroids and therefore the potential for increased risk of systemic side-effects. Consider the benefit of coadministration versus the potential risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.
<u>The following treatments are contraindicated in patients receiving corticosteroid therapy:</u>
- vaccination against smallpox;
- other immunization procedures should not be undertaken in patients receiving corticosteroids (especially high doses), because of possible hazards of neurological complications and lack of antibody response.

However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison disease).
The simultaneous use of diuretics such as the thiazide may increase the risk of glucose intolerance.
Patients receiving both a corticosteroid and an estrogen should be observed for excessive corticosteroid effects.

Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. Often patients receiving treatment with cardiac glycosides, simultaneously use diuretics inducing excretion of potassium from the body. In these cases it is necessary to prescribe preparations that contain potassium. Corticosteroids may enhance the potassium depletion caused by amphotericin B. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely.
Concurrent use of corticosteroids with coumarin-type anticoagulants may increase or decrease the anticoagulant effects, possibly requiring adjustment in dosage. Concerning the patients receiving concurrent treatment with anticoagulants and corticosteroids it is necessary to remember of the possible development of ulceration of the gastrointestinal tract induced by corticosteroids and the risk of internal bleeding.
Corticosteroids may decrease blood salicylate concentrations. With dose reduction of corticosteroids or termination of therapy, patients should be monitored for the possible presence of salicylism. The combination of glucocorticoids with salicylates may increase the frequency and severity of gastrointestinal ulcers.
Combined effects of nonsteroidal anti-inflammatory drugs or alcohol with glucocorticosteroids may result in an increased occurrence or increased severity of gastrointestinal ulceration.
Dosage adjustments of an oral antidiabetic drug or insulin may be necessary when corticosteroids are given to diabetics, given the hyperglycemic effect of glucocorticoids.
Concomitant glucocorticosteroid therapy may inhibit the response to somatotropin. Betamethasone doses higher than 300 to 450 mcg (0.3 to 0.45 mg) per 1 m^2 of body surface area per day should be avoided during the treatment with somatotropin.
Laboratory tests
Corticosteroids may affect the nitroblue tetrazolium test and produce false-negative results. If the patient is treated with corticosteroids, this must be considered when interpreting the parameters and results of biological tests (skin test, thyroid hormone levels, etc.).

4.6. Pregnancy and lactation

Due to lack of adequate teratology studies in humans, glucocorticosteroids should not be given to women during pregnancy, lactation, and woman of childbearing age, with the exception of cases of necessity and only after careful evaluation of the ratio of the expected benefits and possible risks to the mother, the embryo or fetus.
If corticosteroid therapy is indicated in prenatal care, it should weigh the pros and cons and compare the clinical benefit versus adverse effects (including growth inhibition and increased risk of infection).
In some cases, it is necessary to continue corticosteroid treatment during pregnancy or even increase the dose (e.g., in case of corticosteroid replacement therapy).
Intramuscular administration of betamethasone induces significant reduction in the incidence of dyspnea in the fetus when the drug is administered more than 24 hours before delivery (before the 32 week of gestation).
Published data show that the use of prophylactic corticosteroids beyond the 32nd week of gestation is still controversial. Therefore, the physicians should weigh the benefits against the potential hazards to the mother and the fetus when using corticosteroids beyond the 32nd week of gestation.
Corticosteroids are not indicated in the management of hyaline membrane disease after birth.
In the prophylactic treatment of hyaline membrane disease in premature infants, corticosteroids should not be administered to pregnant women with preeclampsia, eclampsia, or evidence of placental damage.
Infants born of mothers who received substantial doses of corticosteroid during pregnancy should be observed carefully for signs of adrenal insufficiency.
When mothers were given betamethasone injections prenatally, the infants had transient suppression of fetal growth hormone and presumably of those pituitary hormones which regulate corticosteroid production by both the definitive and fetal zones of the fetal adrenal glands. However, the suppression of fetal hydrocortisone did not interfere with the pituitary-adrenocortical responses to stress after birth.

Corticosteroids cross the placental barrier and appear in breast milk of nursing mothers.
Because transplacental passage of corticosteroids occurs, newborn and young infants born of mothers who were dosed with corticosteroids throughout most or some portion of their pregnancy should be examined carefully for the possible very rare occurrence of congenital cataracts.
Because of the potential for unwanted adverse effects from Flosteron in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Women who have been on corticosteroids during pregnancy should be monitored during and after labor and delivery for any indication of adrenal insufficiency because of the stresses associated with childbirth.

4.7. Effects on ability to drive and use machines

Should pay particular attention to the possibility of development of CNS effects (euphoria, insomnia) in the case of high doses, as well as visual impairment with prolonged use of the drug.

4.8. Undesirable effects

Adverse reactions to betamethasone, which have been the same as those reported with other corticosteroids, relate both to dose and duration of therapy.
Fluid and Electrolyte Disturbances: sodium retention, potassium loss, hypokalemic alkalosis, fluid retention, congestive heart failure in susceptible patients, hypertension.
Musculoskeletal: muscle weakness, loss of muscle mass, aggravation of myasthenic symptoms in myasthenia gravis, osteoporosis sometimes with severe bone pain and spontaneous fractures (vertebral compression fractures), aseptic necrosis of bone (femoral and humeral heads), tendon rupture, steroid myopathy, pathologic fractures, joint instability.
Dermatologic: skin atrophy, impaired wound healing, thin fragile skin, petechiae, ecchymoses, allergic dermatitis, angioneurotic edema, facial erythema, increased sweating, urticaria.
Gastrointestinal: peptic ulcer with possible subsequent perforation and hemorrhage, pancreatitis, abdominal distention, perforation of the small and large intestine, ulcerative esophagitis, nausea, vomiting, hiccups.
Neurologic: convulsions, vertigo, headache, cephalalgia, increased intracranial pressure (pseudotumor cerebri).
Psychiatric: euphoria, mood swings, personality changes and severe depression, hyperirritability, insomnia, psychotic reactions, especially in patients with anamnesis of psychiatric disturbances, depression.
Ophthalmic: increased intraocular pressure, glaucoma, posterior subcapsular cataracts, exophthalmos, vision blurred.
Endocrine: development of cushingoid state, menstrual disorders, increased requirements of insulin or oral hypoglycemic agents in diabetics, suppression of fetal intrauterine or childhood growth, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, secondary adrenocortical and pituitary insufficiency, particularly in times of stress (as in trauma, surgery or illness).
Metabolic: negative nitrogen balance due to protein catabolism, lipomatosis, weight gain.
Immune system disorders: Corticosteroids may affect the results of skin tests, mask the symptoms of an infection and activate a latent infection, and reduce resistance to infectious agents, in particular to mycobacteria (tuberculosis), Candida albicans and viruses.
Other: anaphylactoid or hypersensitivity reactions and hypotensive or shock-like reactions.
Additional (secondary) adverse reactions related to parenteral corticosteroid therapy: rare instances of blindness associated with intralesional therapy around the face and the head, hyperpigmentation or hypopigmentation, subcutaneous and cutaneous atrophy, sterile abscess, postinjection flare (following intra-articular use), Charcot-like arthropathy.
After repeated intra-articular administration articular lesions can occur. There is a risk of contamination.

4.9. Overdose

Symptoms. Acute overdosage with glucocorticosteroids, including betamethasone, is not expected to lead to a life-threatening situation.
A few days of excessive glucocorticosteroid dosing is unlikely to produce harmful results in the absence of specific contraindications e.g., in patients with diabetes mellitus, glaucoma, or active peptic ulcer, or in patients on medications e.g., digitalis, coumarin-type anticoagulants or potassium-depleting diuretics.
Treatment. Complications resulting from the metabolic effects of the corticosteroid or from deleterious effects of the basic or intercurrent diseases or resulting from drug interactions should be handled as appropriate. Maintain adequate fluid intake and monitor electrolytes in serum and urine, with particular attention to sodium and potassium balance. Treat electrolyte imbalance if necessary.

5. PHARMACOLOGICAL PROPERTIES

According to the ATC classification, betamethasone is classified into the group of corticosteroids for systemic treatment (H02AB01).

5.1. Pharmacodynamic properties

Betamethasone is a synthetic glucocorticoid (9-alpha-fluoro-16-beta-methylprednisolone).
Betamethasone provides potent anti-inflammatory, antiallergic and immunosuppressive effects.
Betamethasone does not have clinically significant mineralocorticosteroid activity. Glucocorticoids cross the cell membrane and bind to specific cytoplasmic receptors. The resulting hormone-receptor complex then enters the nucleus, binds to DNA (chromatin) and stimulates transcription messenger RNA with synthesis protein of different enzymes. The last eventually is responsible for the effects seen with systemic use of glucocorticoids. Besides the impact on the inflammatory and immune processes, glucocorticoids also affect the metabolism of carbohydrates, proteins and lipids. In addition, glucocorticoids act on the cardiovascular system, skeletal muscle and central nervous system.
Influence on inflammatory and immune processes. Anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are at the origin of a very important part of their therapeutic applications. The main aspects of these properties are: decrease in immuno-active cells in the inflammatory focus, decreased vasodilation, stabilization of lysosomal membranes, inhibition of phagocytosis, decreased production of prostaglandins and related substances.
The anti-inflammatory activity of betamethasone is about 25 times higher than that of hydrocortisone, and 8 to 10 times higher than that of prednisolone (on weight basis).
Effect on the metabolism of carbohydrates and proteins. Glucocorticoids stimulate the protein catabolism. In the liver, the released amino acids are converted to glucose and glycogen by the process of gluconeogenesis. The absorption of glucose in peripheral tissues decreases, leading to hyperglycemia and glycosuria, especially in patients with diabetic predisposition.
Effects on the metabolism of lipids. Glucocorticoids have a lipolytic action. The lipolysis is more pronounced in the limbs. In addition, they have a lipogenesis effect which manifests itself especially at the level of the trunk, neck and head. The overall effect results in a redistribution of lipid deposits.
The maximum pharmacological activity of corticosteroids appears later than the peak serum levels are reached, suggesting that most of the effects of these drugs are not based on direct drug action, but on the change in enzyme activity.

5.2. Pharmacokinetic properties

Betamethasone disodium phosphate and betamethasone dipropionate are absorbed from the injection site and induce therapeutic effects and other pharmacological effects at local and systemic levels.
Betamethasone disodium phosphate is highly soluble in water and is metabolized in the body to betamethasone, the biologically active corticosteroid. 2.63 mg betamethasone disodium phosphate represents the equivalent of 2 mg betamethasone.
Sustained activity is provided by betamethasone dipropionate, which is only slightly soluble andbecomes a repository for slow absorption, thereby controlling symptoms over a prolonged period.

Blood values	*Intramuscular injection*	
	Betamethasone sodium phosphate	*Betamethasone dipropionate*
Maximum plasma concentration	1 hour after administration	Slow absorption
Plasma half-life after a single dose	3-5 hours	Progressive metabolization
Excretion	24 hours	More than 10 days
Biological half-life	36-54 hours	

Betamethasone is metabolized in the liver; betamethasone binds primarily to albumin. In patients with hepatic disease, the clearance is slower or delayed.

5.3. Preclinical safety data

The toxicity of betamethasone is relatively low: the LD_{50} values following intramuscular administration in mice, rats and rabbits exceeded 5 mg/kg (approximately 50 times the human therapeutic dose). After subcutaneous administration, the LD_{50} value in rats was 140 mg/kg. A single intramuscular dose of 10 mg/kg did not cause death, but it induced body weight decrease. A dose of 40 mg/kg caused death with the signs of general illness due to general inhibition of the immune defence mechanism. Alopecia and abscesses occurred at the site of intramuscular injection.
Prolonged intramuscular administration of betamethasone disodium phosphate and betamethasone acetate (1:1) to rats at doses 10 to 50 times the human therapeutic dose (0.96-4.8 mg/kg) once weekly induced body weight increase inhibition, thyme atrophy and adrenocortical hyperplasia. When the drug was administered at closer intervals (every third day or daily), the mentioned doses were very dangerous or even fatal due to accumulation, which led to marked catabolic effects as well as to decreased immunological defences. When betamethasone was sprayed onto food pellets at a dose of 0.3 mg/kg and given to guinea pigs, gastrointestinal, kidney and liver injuries were observed. These effects were milder when betamethasone was combined with administration of oligomineral water instead of spring water.
Betamethasone readily crosses the placental barrier. In the fetuses of rats and rabbits, it induced weight reduction, cleft palate, increased Na+-, K+- ATPase activity and produced a variable response to DNA/protein ratio in several organs. Betamethasone was found to stimulate fetal lung maturation when administered to pregnant animals a few days before delivery. FDA classifies betamethasone as category C teratogenic substance.
No mutagenic and carcinogenic effects of betamethasone have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Disodium phosphate dihydrate, sodium chloride, sodium edetate, polysorbate 80, benzyl alcohol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium carboxymethylcellulose, macrogol, concentrated hydrochloric acid, water for injections.

6.2. Incompatibilities

Flosteron suspension can be mixed with a local anesthetic in the syringe; however, compatibility should always be checked.

Concomitant use of local anesthetic is rarely necessary. If coadministration of a local anesthetic is desired, Flosteron may be mixed (in the syringe not the vial) with 1% or 2% lidocaine hydrochloride or procaine hydrochloride, which does not contain parabens. Similar local anesthetics may also be used. Anesthetics containing methylparaben, propylparaben, phenol, etc. should be avoided.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Protect from light, do not store above 25°C.
Keep out of the reach of children.

6.5. Nature and contents of container

Ampoules: 5 ampoules of 1 ml of suspension for injection, in a box.

6.6. Instructions for use and handling

The suspension for injection may be administered intra-articularly, periarticularly, intradermally into skin lesions or as soft tissue infiltration. Flosteron suspension can also be administered as intramuscular injection.
Flosteron suspension can be mixed with a local anesthetic in the syringe.
Flosteron suspension for injection must not be administered intravenously.

7. MARKETING AUTHORIZATION HOLDER

Krka, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORIZATION NUMBER

9. MARKETING AUTHORIZATION DATE

10. DATE OF THE LATEST REVISION OF THE SPC

CONFIDENTIAL