SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CORTENE 4 mg/1 ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betamethasone sodium phosphate..... 5.30 mg
Quantity corresponding to betamethasone..... 4.00 mg
For one ampoule.

Excipient with known effect: sodium
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injectable solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

SYSTEMIC USE
The indications are :

- those of general oral corticosteroid therapy, when the parenteral route is necessary in case of impossibility of the oral route (vomiting, gastric aspiration, disorders of consciousness).

- Conditions requiring a rapid therapeutic effect:

  - allergic:

    - Severe angioedema as an adjunct to antihistamines

    - Anaphylactic shock as an adrenaline supplement.

  - infectious:

    - Severe typhoid fever, particularly with mental confusion, shock, coma,

    - stridulous laryngitis (subglottic laryngitis) in children.

  - neurological:

    - Cerebral edema from tumors, subdural hematoma and cerebral edema related to a toxoplasma abscess.

  - ENT:

    - laryngeal dyspnea

- Antenatal prevention of hyaline membrane disease: induction of fetal maturation.

LOCAL USE
They are the indications for local corticosteroid therapy, when the condition warrants a high local concentration. Any prescription for local injection must take into account the risk of infection, particularly the risk of promoting bacterial proliferation.
This medication is indicated for the following conditions:

- Dermatological: keloid scars

- OPH: periocular injections in certain inflammatory conditions of the anterior segment with involvement of the intermediate uvea.

- ENT: Intra-sinus irrigations in subacute or chronic sinusitis justifying drainage.

- rheumatological:

  - Intra-articular injections: inflammatory arthritis, osteoarthritis flare-ups

  - Periarticular injections: tendinitis, bursitis

  - injections of soft tissues: heel pain, carpal tunnel syndrome, Dupuytren's disease

4.2. Posology and method of administration

This product is not suitable for administration by inhalation via nebulizer.
Anti-inflammatory equivalence (equipotency) for 5 mg of prednisone: 0.75 mg of betamethasone.

SYSTEMATIC USE
IV OR IM INJECTIONS
The posology varies depending on the diagnosis, the severity of the condition, the prognosis, the patient's response, and tolerance to treatment.
1 to 4 ampoules to be repeated within 24 hours, depending on the patient's condition.

LOCAL USE
½ to 2 ampoules depending on the injection site and the condition to be treated.
It is important to avoid injections that are too superficial due to the risk of subcutaneous atrophy.
The injection will only be repeated if symptoms reappear or persist.

4.3. Contraindications

SYSTEMIC USE

- This medication is generally contraindicated in the following situations (however, there is no absolute contraindication for corticosteroid therapy when vital):

  - any infectious condition excluding the specified indications (see section 4.1),

  - certain evolving viral infections (including hepatitis, herpes, chickenpox, shingles),

  - psychotic states not yet controlled by treatment

  - live vaccines,

  - hypersensitivity to any of the excipients listed in section 6.1,

  - coagulation disorders, ongoing anticoagulant treatment in case of intramuscular injection.

- This medicine is generally not recommended in combination with non-antiarrhythmic drugs, which can cause torsades de pointes (see section 4.5).

LOCAL USE

- This medication is contraindicated in the following situations:

  - local or systemic infection, or suspected infection,

  - severe coagulation disorders, ongoing anticoagulant treatment,

  - hypersensitivity to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

Special warnings
SYSTEMATIC USE

- Rare cases of anaphylactoid/anaphylactic reactions, possibly including shock, have occurred in patients treated with parenteral corticosteroids. Appropriate precautions should be taken in patients with a history of allergic reactions to corticosteroids.

- A potentially fatal pheochromocytoma crisis has been reported following the administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or confirmed pheochromocytoma after a careful benefit-risk assessment.

- In the case of gastroduodenal ulcer, corticosteroid therapy is not contraindicated if an anti-ulcer treatment is associated.

In cases of a history of ulcers, corticosteroid therapy may be prescribed, with clinical monitoring and, if necessary, after fibroscopy.

- Corticosteroid therapy can promote the development of various infectious complications, particularly those caused by bacteria, yeasts, and parasites. The development of severe strongyloidiasis is a significant risk.

All subjects coming from an endemic area (tropical, subtropical regions, southern Europe) must have a parasitological examination of stools and systematic eradication treatment before corticosteroid therapy.

The evolving signs of an infection can be masked by corticosteroid therapy.

Before starting treatment, it is important to rule out any possibility of visceral focus, particularly tuberculosis, and to monitor for the appearance of infectious pathologies during treatment.

In cases of past tuberculosis, prophylactic anti-tuberculosis treatment is necessary if there are significant radiological sequelae and if it cannot be ensured that a well-conducted 6-month course of rifampicin treatment has been given.

- The use of corticosteroids requires particularly appropriate monitoring, especially in elderly subjects and in cases of ulcerative colitis (risk of perforation), diverticulitis, recent intestinal anastomoses, renal failure, hepatic failure, osteoporosis, myasthenia gravis.

- Attention is drawn to athletes, as this product contains an active ingredient that may induce a positive result in doping tests.

LOCAL USE
Serious neurological events, some of which have been fatal, have been reported following epidural administration of corticosteroids. Specific reported events include spinal cord infarction, paraplegia, tetraplegia, cortical blindness, and stroke. These serious neurological events have been reported both with and without the use of fluoroscopy. The safety and efficacy of epidural corticosteroid administration have not been established, and corticosteroids are not approved for this use.
In the absence of data concerning the risk of calcifications, it is preferable to avoid the administration of an intradiscal corticosteroid.
Due to potential systemic diffusion, certain contraindications for systemic corticosteroids must be taken into account, particularly if the injections are multiple (several locations) or repeated in the short term:

- certain evolving viral infections (including hepatitis, herpes, chickenpox, shingles),

- psychotic states not yet controlled by treatment

- live vaccines.

Corticosteroid therapy can promote the occurrence of various infectious complications.
Multiple (several locations) or repeated injections in the short term may lead to clinical and biological symptoms of hypercorticism.
Attention is drawn to athletes, as this product contains an active ingredient that may induce a positive result in doping tests.

Precautions for use

SYSTEMATIC USE

Oral treatment will be initiated as soon as possible.

Sodium and water retention is common and partly responsible for a possible rise in blood pressure. Sodium intake will be reduced.

Potassium supplementation is only justified for high-dose treatments, prescribed for a long period of time, or in cases of risk of rhythm disturbances or in combination with hypokalemic treatment.

When corticosteroid therapy is essential, diabetes and hypertension are not contraindications -, but the treatment may lead to their destabilization. Their management should be reassessed.

Patients should avoid contact with individuals who have chickenpox or measles.

LOCAL USE

It is necessary to observe strict aseptic technique.

Local injection of corticosteroids can destabilize diabetes, a psychotic state, and severe hypertension.

Administration should be cautious in patients at high risk of infection, particularly hemodialysis patients or prosthesis wearers.

Do not inject intratendinously.

Visual disturbances may occur during systemic or local corticosteroid therapy (including nasal, inhaled, and intraocular routes). If blurred vision or any other visual symptoms develop during corticosteroid therapy, an ophthalmological examination is required to check for visual disturbances, including cataracts, glaucoma, or rarer conditions such as central serous chorioretinopathy, which have been reported with systemic and local corticosteroid administration.

Results from a multicenter, randomized, placebo-controlled trial with another corticosteroid, methylprednisolone hemisuccinate, showed increased early (2-week) and late (6-month) mortality in patients with traumatic brain injury who received methylprednisolone compared to the placebo group. The causes of death in the methylprednisolone group were not established.

Sodium

This medicine contains less than 1 mmol of sodium (23 mg) per ml, that is to say it is essentially 'sodium free'.

The sodium content of the diluent must be taken into account when calculating the total sodium content of CORTENE 4 mg/1 ml, solution for injection. For detailed information on the sodium content of the solution used to dilute CORTENE 4 mg/1 ml, solution for injection, please refer to the Summary of Product Characteristics of the diluent used.

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

SYSTEMIC USE

Associations not recommended

+ **Drugs that cause torsades de pointes:** astemizole, bepridil, IV erythromycin, halofantrine, pentamidine, sparfloxacin, sultopride, terfenadine, vincamine.

Torsades de pointes (hypokalemia is a contributing factor, as are bradycardia and a pre-existing long QT interval).

Use substances that do not have the disadvantage of causing torsades de pointes in cases of hypokalemia.

+ **CYP3A inhibitors**

It is expected that concomitant administration of CYP3A inhibitors, including products containing cobicistat, will increase the risk of systemic side effects. This combination should be avoided unless the benefits outweigh the increased risk of systemic corticosteroid side effects; in such cases, patients should be monitored for potential systemic corticosteroid side effects.

Associations requiring precautions for use

+ **Acetylsalicylic acid by systemic administration (and by extrapolation, other salicylates)**

Decreased salicylemia during corticosteroid treatment and risk of salicylate overdose after its discontinuation (increased elimination of salicylates by corticosteroids).

Adjust the doses of salicylates during the combination and after stopping treatment with corticosteroids.

+ **Antiarrhythmics causing torsades de pointes:** amiodarone, disopyramide, quinidine, sotalol.

Torsades de pointes (hypokalemia is a contributing factor, as are bradycardia and a pre-existing long QT interval).

Prevention of hypokalemia, and, if necessary, correction; monitoring of the QT interval. In case of torsades de pointes, do not administer antiarrhythmics (transcutaneous pacing).

+ **Oral anticoagulants**

Potential impact of corticosteroid therapy on the metabolism of oral anticoagulants and coagulation factors. Risk of bleeding specific to corticosteroid therapy (gastrointestinal mucosa, vascular fragility) at high doses or with prolonged treatment exceeding 10 days.

When the combination is justified, strengthen monitoring: biological control on the 8th ^{day}, then every 15 days during corticosteroid therapy and after its cessation.

+ **Other hypokalemic agents:** hypokalemic diuretics (alone or in combination), stimulant laxatives, amphotericin B (IV route).

Increased risk of hypokalemia (additive effect).
Monitoring of serum potassium levels, with correction if necessary, to be particularly taken into account in the case of digitalis therapy.
+ **Digitalis**
Hypokalemia promotes the toxic effects of digitalis.
Monitoring of serum potassium levels and, if necessary, ECG.
+ **Heparins (parenteral route)**
Aggravation by heparin of the hemorrhagic risk specific to corticosteroid therapy (digestive mucosa, vascular fragility) at high doses or in prolonged treatment exceeding 10 days.
The association must be justified, and monitoring must be strengthened.
+ **Enzyme inducers:** anticonvulsants: carbamazepine, phenobarbital, phenytoin, primidone, rifampicin.
Decreased plasma concentrations and reduced efficacy of corticosteroids due to increased hepatic metabolism. The consequences are particularly significant in patients with Addison's disease and in transplant recipients.
Clinical and biological monitoring, adjustment of corticosteroid dosage during combination therapy and after discontinuation of the enzyme inducer.
+ **Insulin, metformin, sulfonylureas**
Elevated blood glucose levels, sometimes with ketosis (decreased carbohydrate tolerance due to corticosteroids).
Inform the patient and reinforce self-monitoring of blood and urine, especially at the start of treatment. Adjust the dosage of the antidiabetic medication if necessary during corticosteroid treatment and after its discontinuation.
+ **Isoniazid** (described for prednisolone)
Decreased plasma concentrations of isoniazid. Proposed mechanism: increased hepatic metabolism of isoniazid and decreased metabolism of glucocorticoids.
Clinical and biological monitoring.

Associations to consider

+ **Antihypertensives**
Decreased antihypertensive effect (sodium and water retention caused by corticosteroids).
+ **Interferon alpha**
Risk of inhibition of the action of interferon.
+ **Live attenuated vaccines**
Risk of potentially fatal systemic disease. This risk is increased in individuals already immunocompromised by the underlying disease.
Use an inactivated vaccine when available (poliomyelitis).
LOCAL USE
The risk of interactions between glucocorticoids and other medications is exceptional when administered by local injection under normal circumstances. These risks should be considered in the case of multiple injections (several sites) or repeated injections in the short term.

4.6. Fertility, pregnancy and breastfeeding

SYSTEMIC USE

Pregnancy

In animals, experimentation highlights a teratogenic effect that varies depending on the species.
In humans, there is placental transfer. However, epidemiological studies have not detected any malformation risk associated with taking corticosteroids during the first trimester.
In cases of chronic diseases requiring treatment throughout pregnancy, a slight delay in intrauterine growth is possible. Neonatal adrenal insufficiency has been observed in rare cases following high-dose corticosteroid therapy.
Studies have shown an increased risk of neonatal hypoglycemia following antenatal administration of a short course of betamethasone to women at risk of late preterm delivery.
It is justified to observe a period of clinical (weight, diuresis) and biological monitoring of the newborn.
Consequently, corticosteroids may be prescribed during pregnancy if needed.

Breastfeeding

In the case of treatment with high doses and on a chronic basis, breastfeeding is not recommended.
LOCAL USE
The risk of systemic corticosteroids should be considered in cases of multiple (several sites) or repeated injections in the short term: with systemic corticosteroids, a slight delay in intrauterine growth is possible. Neonatal adrenal insufficiency has been observed in rare cases following high-dose corticosteroid therapy. Breastfeeding is not recommended in cases of high-dose treatment.

4.7. Effects on the ability to drive vehicles and use machinery

Not applicable.

4.8. Undesirable effects

SYSTEMIC USE
Rare cases of anaphylactic reactions have been reported in patients treated with parenteral corticosteroids (see section 4.4). Cardiac arrhythmias related to intravenous administration have also been described.
Other effects:

- Hydro-electrolytic disorders: hypokalemia, metabolic alkalosis, sodium and water retention, arterial hypertension, congestive heart failure.

- Endocrine and metabolic disorders: iatrogenic Cushing's syndrome, inertia of ACTH secretion, sometimes permanent adrenocortical atrophy, decreased glucose tolerance, revelation of latent diabetes, growth arrest in children, menstrual irregularities.

- Musculoskeletal disorders: muscle atrophy preceded by muscle weakness (increased protein catabolism), osteoporosis, pathological fractures in particular vertebral compression fractures, aseptic osteonecrosis of the femoral heads.

- Digestive disorders: hiccups, gastroduodenal ulcers, small bowel ulceration, perforations and digestive hemorrhages, acute pancreatitis have been reported, especially in children.

- Skin disorders: acne, purpura, ecchymosis, hypertrichosis, delayed wound healing and angioedema.

- Neuropsychiatric disorders:

    - Frequently: euphoria, insomnia, excitement.

    - rarely: manic episodes; confusional or delirious states, convulsions.

    - Depressive state upon cessation of treatment.

- Eye disorders: certain forms of glaucoma and cataracts; blurred vision (see also section 4.4).

LOCAL USE
Systemic side effects of glucocorticoids have a low risk of occurring after local administration, given the low blood levels, but the risk of hypercorticism (sodium and water retention, imbalance of diabetes and high blood pressure...) increases with the dose and frequency of injections.

- Risk of local infection (depending on the injection site): arthritis,…

- Localized atrophy of muscle, subcutaneous, and cutaneous tissues. Risk of tendon rupture if injected into the tendons.

- acute microcrystalline arthritis (with microcrystalline suspension) of early onset,

- local calcifications,

- local and general allergic reactions including angioedema

- Flushing: headaches and hot flashes may occur. They usually disappear within a day or two;

- Blurred vision (see also section 4.4) has been reported with the use of corticosteroids (frequency not known).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals report any adverse effects suspected unwanted substance via the FRILAB declaration form available under the tab pharmacovigilance information from the website : www.frilab.ch

4.9. Overdose

In case of acute overdose, administer appropriate symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: corticosteroids for systemic use not combined, ATC code: H02AB01 .
Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including betamethasone, are used primarily for their anti-inflammatory effect. At high doses, they suppress the immune response. Their metabolic and sodium-retaining effects are less pronounced than those of hydrocortisone.

5.2. Pharmacokinetic properties

Parenteral absorption of the injectable form is very rapid.
Part of betamethasone is bound to plasma proteins, and only the free fraction has pharmacological activity.
Betamethasone is metabolized in the liver and eliminated by the kidneys. The plasma half-life of betamethasone is approximately 5 hours; its biological half-life is 36 to 54 hours.
Betamethasone passes into breast milk and across the placenta.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dibasic sodium phosphate, disodium edetate dihydrate, sodium metabisulfite, sodium hydroxide, water for solution for injection.

6.2. Incompatibilities

In the absence of compatibility studies, this medicine should not be mixed with other medicines.

6.3. Shelf life

Before opening: 2 years.
Once opened, the product must be used immediately.

6.4. Special precautions for storage

Store at a temperature not exceeding 30°C and away from light.

6.5. Nature and contents of container

1 ml in ampoule, box of 3.

6.6. Special precautions for disposal and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

FRILAB SA
17, rue des Pierres du Niton
1207 Geneva
SWISS

8. MANUFACTURER

MJ BIOPHARM PVT.LTD.
PLOT NO.L7,MIDC INDUSTRIAL AREA, TALOJA
RAIGAD 410208 MAHARASHTRA STATE, INDIA

9. DATE OF REVISION OF THE TEXT

June 2024

10. DOSIMETRY

Not applicable.

11. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I