

DEFAL

1. PRODUCT NAME

Defal 6 mg tablets
Defal 30 mg tablets
Defal drops 22,75 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Defal 6 mg tablets: each tablet contains 6 mg deflazacort.
Excipients: each tablet contains 153.0 mg lactose monohydrate and 10.0 mg maize starch

Defal 30 mg tablets: each tablet contains 30 mg deflazacort.
Excipients: each tablet contains 313.0 mg lactose monohydrate and 10.0 mg maize starch

Defal drops 22,75 mg/ml.
Each ml of suspension contains 22,75 mg of deflazacort, or each drop of suspension contains 1 mg of deflazacort.
Excipients with a known effect: each ml of suspension contains 100 mg of sorbitol

See section 6.1 for full list of excipients.

3. PHARMACEUTICAL FORM

Tablets

Deflazacort FAES 6 mg tablets: round, non-coated white tablets, with a cross engraved on one side and the number 6 on the other.

Deflazacort FAES 30 mg tablets: round, non-coated white tablets, with a cross engraved on one side and the number 30 on the other.

Each tablet can be broken into two halves.

Drops

Defal drops Homogeneous suspension of a whitish colour

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatic and collagen disorders: treatment of acute episodes and/or maintenance therapy in rheumatoid arthritis, psoriatic arthritis when conservative treatment has been ineffectual; polymyalgia rheumatica; acute rheumatic fever; systemic lupus erythematosus; severe dermatomyositis; periarteritis nodosa; cranial arteritis and Wegener's granulomatosis.

Dermatological disorders: Pemphigus, bullous pemphigoid, exfoliative dermatitis in general, severe erythema multiforme, erythema nodosum and severe psoriasis.

Allergies: Bronchial asthma resistant to conventional treatment.

Lung disorders: pulmonary sarcoidosis, extrinsic allergic alveolitis (pneumoconiosis due to inhalation of organic dust), desquamative interstitial pneumonia (idiopathic pulmonary fibrosis).

Ocular pathologies: choroiditis, chorioretinitis, iritis and iridocyclitis.

Haematological disorders: idiopathic thrombocytopenia, haemolytic anaemia and palliative treatment of leukaemia and lymphomas.

Gastrointestinal and hepatic pathologies: ulcerative colitis, Crohn's disease and active chronic hepatitis.

Renal disorders: nephrotic syndrome.

4.2. Dosage and method of administration

The initial dose varies between 6 and 90 mg p.d. for adults, and 0.25 and 1.5 mg/kg for children, depending on the severity and progress of the disorder in each case. This initial dose may be maintained or modified, until the required clinical response is obtained.

The maintenance dose should always be the minimum dose required to control symptoms. Reductions in the dose should be applied gradually, to allow for the recovery of the hypothalamus-hypophysary-adrenal axis function.

Defal oral drops suspension has a special interest in pediatrics, given the ease of administration and its acceptance, even in infants (1 drop contains 1 mg of deflazacort). No clinical data are available on the efficacy of deflazacort in children younger than 2 months.

Method of administration:

Oral way.

In suspension oral drops, the bottle should be shaken before use. The suspension to be administered may be diluted immediately before making sugar water or non-carbonated beverages.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

The use of corticoids for longer than the duration of replacement treatment or short-term emergency therapy is contraindicated in the following cases:

Peptic ulcer, bacterial and viral infections, active tuberculosis, ocular herpes, shingles (viremic phase), chickenpox, systemic mycotic infections; and in pre- and post-vaccination periods.

4.4. Special warnings and special precautions for use

One 6 mg deflazacort tablet is therapeutically equivalent to approximately 5 mg prednisone. However, it should be taken into account that corticosteroid requirements vary and, accordingly, dosages must be set individually, taking the patient's pathology and response to therapy into account.

Special care should be taken in the following cases before deciding to initiate treatment with glucocorticoids:

heart disease (except for active rheumatic carditis), high blood pressure, thromboembolic disorders, infections (when the indicated anti-infective therapy should be applied), gastritis or oesophagitis, ulcerative colitis when there is a risk of perforation or pyogenic infection, recently-performed intestinal

anastomosis, diabetes mellitus, emotional instability or psychotic tendencies, epilepsy, glaucoma, hypothyroidism and cirrhosis (in these latter two cases, the effect of the glucocorticoids may be enhanced).

Doses may need to be increased in stressful situations, such as infections, injuries or surgery.

Over prolonged treatment and at high doses, the electrolyte balance should be monitored and, if necessary, sodium and potassium intake adjusted.

After treatment is discontinued, secondary suprarenal insufficiency may persist for months. Accordingly, prolonged treatment should not be withdrawn suddenly, in order to avoid the risk of corticoid withdrawal syndrome. For any stressful situations which may arise during this period, the indicated hormonal treatment should be applied. In these situations, mineralcorticoid secretion may become compromised, and it may be necessary to supply concomitant salts and/or mineralcorticoids.

Prolonged use of glucocorticoids in children may inhibit growth and development.

Warnings on excipients

Tablets 6 mg and 30 mg:

These medications contain lactose. Patients with hereditary problems of galactose intolerance, Lapp lactase deficiency (failure observed in certain populations of Lapland) or glucose-galactose malabsorption should not take this drug product.

Drops:

This medicine contains sorbitol. Patients with hereditary fructose intolerance should not take this medicine.

This product contains lactose. Consult your doctor before taking this medicine if you may be intolerant to certain sugars.

Notice to athletes:

this medicine contains deflazacort. Deflazacort may test positive in doping controls.

4.5. Interactions

Concomitant administration of this medicine with non-steroid anti-inflammatory drugs may increase the risk of suffering from gastrointestinal ulcers.

Levels of salicylates in the blood may drop when using glucocorticoids, and rise spontaneously to toxic levels when treatment is interrupted.

Potassium depleting diuretics may enhance the hypokalaemic action of glucocorticoids, while digitalis drugs can increase the possibility of hypokalaemia-associated arrhythmia. It may be necessary to increase the dose of anti-diabetic drugs.

Rifampicin, barbiturates and phenytoin may accelerate glucocorticoid metabolism. Accordingly, addiction to or withdrawal from said drugs may require an adjustment to the corticoid dose.

In patients with myasthenia gravis, anticholinesterase drugs may interact with glucocorticoids and lead to severe muscular fatigue.

In patients under treatment with systemic corticoids, the use of non-depolarising muscle relaxants may lead to prolongation of the relaxant effect.

Glucocorticoids decrease the immunological response to vaccines and toxoids, and may also enhance germ growth in attenuated live vaccines.

Patients with hypoprothrombinemia are advised to be careful when associating acetylsalicylic acid and corticosteroids.

Levels of protein-linked iodine and thyroxine (T4) in plasma may decrease, as may I131 uptake.

Corticosteroids may increase or decrease the effects of anti-coagulants.

The effects of corticosteroids may be enhanced in women taking oestrogen or oral contraceptives; in these cases, the corticosteroid dose may need to be reduced.

4.6. Pregnancy and lactation

Use during pregnancy: Sufficient evidence is not available with regard to the safety of this medicine in pregnant women. Corticosteroids have been observed to cause foetal abnormalities in animals, including cleft palate and intrauterine growth retardation.

Consequently, there is a slight risk to the foetus and, when assessing the use of deflazacort in pregnant humans, the benefits of treatment need to be balanced against the possible risks.

Breast feeding: Glucocorticoids are excreted in breast milk. This may cause growth retardation and inhibit endogenous steroid production. Accordingly, their use during breastfeeding is not advised.

4.7. Effects on the ability to drive and operate machinery

No data available.

4.8. Adverse reactions

Immune system disorders: Greater susceptibility to infections

- Gastrointestinal disorders:
Greater susceptibility to infections, dyspepsia, peptic ulcer, perforated peptic ulcer, gastrointestinal bleeding, acute pancreatitis (particularly in children).
- Nervous system disorders:
Headaches, dizziness, light-headedness, insomnia, mood swings, depression, pseudotumor cerebri in children
- Disorders of the skin and subcutaneous tissue:
Thinning of the skin, stretch marks, acne.
- Cardiac and vascular disorders:
Sodium retention and high blood pressure, oedema and heart failure, intracranial hypertension, potassium depletion,
- Endocrine disorders:
Relative adrenal insufficiency, which may persist up to 1 year after discontinuation of prolonged treatment. Cushingoid weight gain and moon face, amenorrhea, diabetes mellitus, suppression of the hypothalamus-hypophysary-adrenal axis function, growth retardation in children,
- Musculoskeletal and connective tissue disorders:
myopathy (in patients treated with systemic corticosteroids, particularly during treatment with high doses and after prolonged treatment, the use of non-polarising muscle relaxants may trigger acute myopathy), avascular necrosis, clots, osteoporosis.
- Eye disorders:
posterior subcapsular cataracts, particularly in children, and increased ocular pressure.

4.9. Overdose

No cases of deflazacort intoxication have been described; in its event, symptomatic treatment is advised.

High doses of corticosteroids, taken orally over a prolonged period of time, may suppress hypothalamus-hypophysary-adrenal axis function.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: systemic corticosteroids, ATC code: H02AB13.

Deflazacort is a synthetic glucocorticoid. It is similar to other corticoids in that it possesses anti-inflammatory properties, but has a different safety profile due to its reduced activity on bone and hydrocarbon metabolism.

When the physiological dose is exceeded, all glucocorticoids involve negativisation of the calcium balance, by means of reducing its intestinal absorption and/or increasing its elimination via the urine: this initially leads to a gradual loss of bone mass, which may progress to osteoporosis.

In dual photon absorptiometry and iliac crest biopsy studies carried out on humans, in comparison with other glucocorticoids deflazacort was observed to interfere less with calcium absorption and urinary excretion of calcium, with the subsequent effect on bone reabsorption shown by a less marked reduction in the volume of the trabecular bone and bone mineral content. Moreover, in 3 clinical studies carried out on 143 children under treatment up to 26 months, deflazacort was observed to interfere less with their growth.

On the other hand, natural and synthetic corticoids tend to decrease glucose tolerance and clinically unmask latent diabetes mellitus, requiring treatment for diabetes to be instituted, or to exacerbate already clinical diabetes, consequently requiring an increase in the habitual dose of diabetes drugs. In comparative studies, the interference of deflazacort on glucid metabolism has been observed to be significantly lower than other glucocorticoids, with better metabolic control and better glucose tolerance in diabetic patients.

5.2. Pharmacokinetic properties

Deflazacort taken orally is absorbed well and immediately transformed by plasma esterases into its active metabolite deflazacort 21-OH. This metabolite reaches maximum plasma levels in 1.5-2 hours. The metabolite, 40% of which is bound to plasma proteins, has no affinity for transcortin. The average plasma half-life of deflazacort 21-OH is 1.1-1.9 hours.

It is eliminated mainly through the kidneys, 70% of the compound being excreted within 8 hours of being taken. The remaining 30% is eliminated via faeces.

Deflazacort 21-OH is extensively metabolised, only 5% of urinary excretion consisting of 21-OH deflazacort; deflazacort 6-beta-OH metabolites make up a third of urinary excretion.

5.3. Preclinical safety data

Acute and chronic toxicology studies show findings similar to those found for other corticosteroids at equivalent anti-inflammatory doses. The teratogenic effects observed in laboratory animals are those observed for other corticoids.

Doses of DL50 (4000-5200 mg/kg) given to mice, rats and dogs were 3000-4000 times higher than the maximum daily clinical doses given to humans. Two full toxicity studies on oral doses repeated over 12 months, carried out on rats and macaca fascicularis monkeys and backed up by short-term studies, showed changes related with the typical treatment of glucocorticoids.

As with other glucocorticoids, deflazacort showed dose-dependent teratogenic effects in rats and rabbits at very high doses, with no genotoxic effects being observed throughout an extensive battery of mutagenic tests in vivo and in vitro. Deflazacort was not observed to induce or stimulate the development of tumours in mice.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Defal 6 and 30 mg Tablets

Lactose monohydrate, corn starch, microcrystalline cellulose, magnesium stearate.

Defal drops

Aluminium magnesium silicate, Carboxymethylcellulose sodium, Benzyl alcohol, Sorbitol 70%, Polysorbate 80, Acetic acid, glacial, Water, purified.

6.2. Incompatibilities

None described.

6.3. Shelf life

Defal 6 mg and 30 mg Tablets

Three years.

Defal drops

Two years

6.4. Special precautions for storage

No special storage precautions are required.

6.5. Nature and contents of container

Defal tablets are packaged in a blister made of PVC and aluminium-PVC foil.

Defal 6 mg tablets: packages containing 20 or 500 tablets.

Defal 30 mg tablets: packages containing 10 or 500 tablets.

Defal drops is packed in an amber glass container of 20 ml with a cap with aluminium seal including a glass dropper. The content of the container is 13 ml of oral drops in suspension.

6.6. Special precautions for disposal

No special precautions.

7. HOLDER OF THE marketing authorisation

FAES FARMA, S.A.
Máximo Aguirre, 14
48940 Leioa (Vizcaya)

8. MARKETING AUTHORIZATION NUMBER(S)

Defal 6 mg Tablets: N° Reg. AEM: 57.817
Defal 30 mg Tablets: N° Reg. AEM: 57.816
Defal Drops 22,75 mg/ml: N° Reg. AEM: 61.049

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Tablets 6 mg and 30 mg:

Date of first authorisation: 2 March 1990
Date of last renewal: September 2009

Drops:

Date of first authorisation: 4 November 1996
Date of last renewal: September 2009

10.DATE OF THIS VERSION

September/1999.