

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doloproct 0.1 % + 2 % rectal cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g Doloproct rectal cream contains:

1 mg fluocortolone pivalate and
20 mg lidocaine hydrochloride (water free).

Excipients with known effect:

60 mg Cetostearyl alcohol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal cream

White, opaque cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of pain and inflammation in adults for:

haemorrhoidal disease,
non-infectious proctitis and
anal eczema.

4.2 Posology and method of administration

Posology

Doloproct rectal cream should be applied twice a day, once in the morning and once in the evening (approximately up to 1 g cream per application). In the initial days of use, it can be applied three times daily. With improvement of symptoms, a single daily application is often sufficient.

The total duration of treatment should not exceed 2 weeks.

Paediatric population

Doloproct is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Method of administration

It is advisable to administer Doloproct after defecation. The anal region should be cleaned thoroughly prior to use.

A finger-tip unit of Doloproct rectal cream is applied to the anal region with a finger, using the finger tip to overcome the resistance of the sphincter.

A finger-tip unit is the amount of rectal cream expressed from the tube and applied from the distal skin-crease to the tip of the index finger of an adult.

If Doloproct rectal cream is to be applied intra-rectally, the applicator provided has to be screwed onto the tube and the tip inserted into the anus. A small quantity of cream can then be applied by exerting slight pressure on the tube (for use and cleaning of the applicator see section 6.6).

4.3 Contraindications

Doloproct is contra-indicated in case of topical infections in the affected area and if symptoms of the following disorders are present in the affected area:

- specific skin lesions (syphilis, tuberculosis)
- chickenpox
- vaccination reactions
- herpes genitalis

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

4.4 Special warnings and precautions for use

Since Doloproct contains the active substance lidocaine and approximately 30 % of the dose applied is systemically available, this should be considered in patients taking medicines to treat irregular heart beat (arrhythmia).

Care should be taken to ensure that Doloproct does not come into contact with the eyes. It is advisable to wash one's hands thoroughly after use.

Visual disturbance:

Visual disturbance may be reported with systemic and topical 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 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.

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

The excipients (polysorbate 60, sorbitan stearate, paraffin white soft and paraffin liquid) in Doloproct rectal cream may reduce the effectiveness of latex products such as condoms.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of Doloproct in pregnant women. Animal experimental studies with glucocorticosteroids have shown reproductive toxicity (see section 5.3).

A number of epidemiological studies suggest that there could possibly be an increased risk of oral clefts among newborns of women who were treated with systemic glucocorticosteroids during the first trimester of pregnancy. Oral clefts are a rare disorder and if systemic glucocorticosteroids are teratogenic, these may account for an increase of only one or two cases per 1000 women treated while pregnant.

Data concerning topical glucocorticosteroid use during pregnancy are insufficient, however, a lower risk might be expected since systemic availability of topically applied glucocorticosteroids is very low. As a general rule, topical preparations containing glucocorticosteroids should not be applied during the first trimester of pregnancy.

Breast-feeding

The clinical indication for treatment with Doloproct rectal cream must be carefully reviewed and the benefits weighed against the risks in pregnant and lactating women. In particular, prolonged use must be avoided.

Fertility

No investigation on the potential effects of fluocortolone or its esters has been performed. Studies in animals have shown no effects on fertility for lidocaine hydrochloride (see section 5.3).

4.7 Effects on ability to drive and use machines

Doloproct has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The incidence of the undesirable effects was calculated from pooled clinical trial data involving 661 patients.

Eye disorders

Not known (cannot be estimated from the available data)

Vision, blurred (see also section 4.4)

Skin and subcutaneous tissue disorders

Uncommon ($\geq 1/1,000$ to $< 1/100$):

Allergic skin reactions to any of the ingredients.

General disorders and administration site conditions

Common ($\geq 1/100$ to $< 1/10$):

Application site burning.

Uncommon ($\geq 1/1,000$ to $< 1/100$):

Application site irritation.

After prolonged therapy with Doloproct rectal cream (more than four weeks), there is a risk that the patient may develop local skin alterations, such as atrophy, striae or telangiectasias.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in <http://www.medicinesauthority.gov.mt/adrportal>.

4.9 Overdose

Symptoms

The results of investigations of the acute toxic potential of the active substances in Doloproct show that there is no risk of acute toxic symptoms following accidental overdosage during a single rectal or perianal application of Doloproct to be expected.

After accidental oral ingestion of the preparation (e.g. ingestion of several grams of cream), the main symptoms to be expected are likely to be systemic effects of lidocaine hydrochloride, which, depending on dose, may be manifested in the form of severe cardiovascular symptoms (depression of cardiac function or cardiac arrest in extreme cases) or symptoms related to the central nervous system (convulsions, dyspnoea or respiratory failure in extreme cases).

Management

The management of an overdose includes close monitoring of vital functions, supportive care including oxygen supply, and symptomatic treatment of central and cardiovascular symptoms e.g. including short acting barbiturates, beta-sympathomimetica, atropine. Dialysis is of negligible value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Vasoprotectives. Agents for treatment of haemorrhoids and anal fissures for topical use.

ATC code: C05AA08

Doloproct cannot remove the causes of development of haemorrhoidal disease, proctitis and anal eczema. A post-marketing study of Doloproct cream in comparison to vehicle and fluocortolone pivalate monotherapy was performed in 241 patients with rectal bleeding due to haemorrhoid

disease. Since efficacy results could not be evaluated properly, superiority of the fixed combination of active substances as present in Doloproct compared to fluocortolone pivalate monotherapy has not been established yet.

If haemorrhoidal disease is accompanied by inflammation and eczematous skin symptoms, combined use of Doloproct rectal cream and Doloproct suppositories can be recommended.

- Fluocortolone pivalate

Fluocortolone pivalate inhibits inflammatory and allergic skin reactions, and alleviates subjective complaints such as pruritus, smarting, and pain. The substance reduces dilatation of the capillaries, oedema of the interstitial cells and infiltration of the tissues. Capillary multiplication is inhibited.

- Lidocaine hydrochloride

Lidocaine hydrochloride is a standard local anaesthetic which has been in use for many years. As it has analgesic and antipruritic effects, it has been found to be effective when used in suppositories and creams designed for the treatment of haemorrhoidal disease. The suppression of pain and pruritus is the result of the inhibition of afferent nervous pathways.

5.2 Pharmacokinetic properties

After rectal application of the cream in healthy male volunteers, a maximum of 15 % of the dose of fluocortolone pivalate and 30 % of the dose of lidocaine hydrochloride was systemically absorbed (radiolabelled active substances).

5.3 Preclinical safety data

- Acute toxicity

Based on the results of conventional studies into the acute toxicity, no specific risk to humans is to be expected after the therapeutic use.

- Subchronic / chronic toxicity

In order to assess the systemic tolerance following repeated application of the active substances toxicity studies using dermal and rectal routes of application were carried out. The most prominent effects were the typical signs of overdose of the glucocorticosteroid or the local anaesthetic.

Data obtained concerning the absorption and bioavailability of the two active substances indicate, however, that no pharmacodynamically effective systemic burden is to be expected if Doloproct is used according to prescription.

- Reproductive toxicity

Based on embryotoxicity studies with fluocortolone / fluocortolone hexanoate and lidocaine hydrochloride, embryotoxic / teratogenic effects in humans are not expected to occur with the use of Doloproct.

There are hints from animal experiments that administration of systemic glucocorticoids during pregnancy might contribute to postnatal effects such as cardiovascular and/or metabolic diseases, and to permanent changes in density of glucocorticoid receptors, in neurotransmitter turnover and in behaviour in the offspring.

In general, glucocorticosteroids lead to embryotoxic and teratogenic effects (e.g. oral clefts, skeletal malformations, intrauterine growth retardations, embryoletality) in the appropriate test systems. In view of these findings, particular care should be taken when prescribing Doloproct during pregnancy. The results of epidemiological studies are summarized in section 4.6 .

– Fertility

The potential impact of Doloproct rectal cream on fertility has not been investigated.

Lidocaine hydrochloride was subcutaneously given to rats at a dose level of 10 mg/kg bodyweight for a period of 8 months. During this time the animals were mated three times and no effects on fertility was reported.

No investigation on the potential effects of fluocortolone or its esters on fertility has been performed in animals.

– Genotoxicity and carcinogenicity

In-vitro and *in-vivo* studies gave no relevant indication on a genotoxic potential of fluocortolone.

Specific tumorigenicity studies with fluocortolone / fluocortolone pivalate have not been carried out. On the basis of the pharmacodynamic mode of action, the lack of evidence of a genotoxic potential, the chemical structure and the results of chronic toxicity studies, there is no suspicion of a tumorigenic potential for fluocortolone pivalate.

There is at present no suggestion that lidocaine might be mutagenic. However, there are signs that a metabolite of lidocaine, 2,6-xylidine, that occurs in the rat and possibly also in humans, might have a mutagenic effect. These signs are based on *in-vitro* tests in which this metabolite was used at very high, almost toxic concentrations.

In a carcinogenicity study in rats with transplacental exposure and 2 years postpartum treatment with high doses of 2,6-xylidine both, malignant and benign tumors, especially in the nasal cavity (ethmoturbinal) were observed in a highly sensitive test system. It does not appear absolutely improbable that this may be relevant to humans. For this reason lidocaine should not be administered at high doses for prolonged periods.

– Local tolerance

Investigations into the local tolerance on the skin and the mucosa did not reveal any changes beyond those topical side-effects known for glucocorticoids.

Experimental investigations for detection of possible sensitizing effects have not been carried out with the active substances of Doloproct. Data in the literature suggest that the active substances as well as the components of the formulation base could be responsible for the allergic skin reactions observed only sporadically following use of Doloproct. However, Doloproct is only expected to provoke contact allergies in rare cases.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 60
Sorbitan stearate
Cetostearyl alcohol
Paraffin, liquid
Paraffin, white soft
Sodium edetate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dodecahydrate
Benzyl alcohol
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

After first opening of the container the in-use stability is 4 weeks.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminum tube, coated with epoxy resin, with a polyethylene screw-cap and a polypropylene applicator.

Pack sizes

10 g

15 g

30 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Use of the applicator:

Do not use the applicator if damaged. Screw the applicator completely on the tube.

After each use, clean externally the applicator with a paper towel, then remove the remaining product in the applicator with a cotton swab and clean it again with a paper towel. Rinse the applicator under warm water for about 1 minute and dry externally the applicator with towel paper.

7. MARKETING AUTHORISATION HOLDER

LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

MA024/01701

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 September 2005

Date of latest renewal: 24 August 2011

10. DATE OF REVISION OF THE TEXT

27th January 2020