

# DOLOPROCT<sup>®</sup>

Rectal cream or suppositories containing fluocortolone pivalate and lidocaine hydrochloride

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## Presentation

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1 g of white, opaque rectal cream contains 1 mg fluocortolone pivalate and 20 mg lidocaine hydrochloride (anhydrous).

1 yellowish-white suppository contains 1 mg fluocortolone pivalate and 40 mg lidocaine hydrochloride (anhydrous).

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## Uses

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### *Actions*

Fluocortolone exerts an anti-inflammatory, antiallergenic and antipruritic effect. Capillary dilatation, intercellular edema and tissue infiltration regress; capillary proliferation is suppressed.

### *Pharmacodynamic Properties*

Pharmacotherapeutic group: topical antihemorrhoidal agent

ATC code: C05 AX 03

- Fluocortolone pivalate

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

- Lidocaine hydrochloride

Lidocaine hydrochloride is a standard local anesthetic 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 hemorrhoidal complaints. The suppression of pain and pruritus is the result of the inhibition of afferent nervous pathways.

### *Pharmacokinetic Properties*

The DOLOPROCT rectal cream/suppositories are topical preparations which display their anti-inflammatory and analgesic effects at the site of application.

The active ingredients diffuse out of the preparations into the inflamed tissue, are partially absorbed, distributed by the circulatory system, metabolised and finally excreted. In order to obtain a local therapeutic effect, pharmacologically effective plasma levels are not required.

In order to assess the risk of systemic effects after rectal application of the DOLOPROCT preparations, a series of volunteer studies were performed.

- Fluocortolone pivalate

After single rectal application of 1 g cream or one suppository to volunteers, the corticosteroid was incompletely absorbed.

During application of 2 suppositories 3 times daily to volunteers for 4 weeks, no systemically effective fluocortolone plasma levels have been achieved at steady-state.

Corticosteroid esters such as fluocortolone pivalate are hydrolysed into the free steroid and the respective fatty acid during absorption or immediately afterwards by ubiquitous esterases.

Fluocortolone is excreted in the form of its metabolites mainly in the urine. After intravenous administration, plasma half-lives of between 1.3 hours and 4 hours have been determined for fluocortolone and its metabolites.

- Lidocaine-HCl

Lidocaine is also incompletely absorbed and bioavailable after rectal application of the cream and suppository (30% and 24% of the dose respectively).

After intravenous administration lidocaine is eliminated from the plasma with a half-life of 1-2 hours. Lidocaine is metabolised in humans by oxidative N-desalkylation, hydrolysis of the amide bond and hydroxylation of the aromatic ring to 4-hydroxy-2,6-xylidine, which represents the major metabolite (about 70% of the dose) in the urine.

### ***Indications***

For the symptomatic relief of pain, swelling, burning and itching associated with:

- hemorrhoids
- proctitis
- anal eczema (DOLOPROCT Cream only)

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### **Dosage and Administration**

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The anal region should be cleaned thoroughly before using DOLOPROCT, which is best applied after defecation. There is usually a rapid improvement, but this should not mislead one into stopping treatment too soon. To avoid relapses, DOLOPROCT should be continued for at least one week, though less frequently (rectal cream once a day or one suppository every other day), even when the symptoms have completely disappeared. However, duration of treatment with DOLOPROCT should not exceed 2 weeks.

DOLOPROCT cannot remove the causes of development of hemorrhoids, proctitis or anal eczema.

If hemorrhoids are accompanied by inflammation and eczematous skin symptoms, combined use of DOLOPROCT rectal cream and DOLOPROCT suppositories can be recommended.

### ***Rectal Cream***

Generally, DOLOPROCT rectal cream is applied twice daily, once in the morning and once in the evening. In the initial days of use, it can be applied three times daily. With improvement of symptoms, a single daily application is often sufficient. A little cream (about the size of a pea) is smeared around the anus and in the anal ring with a finger, using the fingertip to overcome the resistance of the sphincter. If the cream is to be used within the rectum, the enclosed applicator should be screwed onto the tube and inserted into the anus. A small amount of cream can then be applied in the rectum by squeezing the tube lightly.

However, for very inflamed and hence painful lesions, it is advisable initially to apply the cream internally with the finger. Protruding lumps should be smeared thickly and pressed carefully back with the finger.

### ***Suppositories***

In general, one suppository should be inserted high into the rectum twice daily, once in the morning and once in the evening. If symptoms are severe, one suppository can be inserted three times daily in the first three days. With increasing improvement of symptoms, just one suppository per day or every second day is sufficient in many cases.

The consistency of suppositories that have become soft due to heat can be restored by placing them in cold water before the covering is removed.

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## **Contraindications**

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DOLOPROCT should not be used during the first trimester of pregnancy.

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 processes in the area to be treated (syphilis, tuberculosis)
- viral diseases (e.g. vaccinia, chickenpox)
- vaccination reactions

DOLOPROCT should not be used in the case of known hypersensitivity to any of the ingredients.

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## Warnings and Precautions

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In the event of fungal involvement, antimycotic therapy is required in addition to the use of DOLOPROCT.

Care must be taken to ensure that DOLOPROCT does not come into contact with the eyes. Careful hand washing after use is recommended.

Treatment of children and adolescents is not recommended as no clinical studies in children or adolescents have been conducted.

If DOLOPROCT rectal cream is applied to the genital or anal areas, the excipients, paraffin and soft paraffin, may reduce the strength of latex condoms used concomitantly, thus impairing the safety of the condoms.

### ***Preclinical Safety Data***

- Acute toxicity

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

- Subchronic/chronic toxicity

In order to assess 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 anesthetic.

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

Animal experimental studies suggest 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. The relevance of these findings in humans is unknown. Further animal studies have shown that glucocorticosteroids lead to embryotoxic and teratogenic effects (e.g. oral clefts, skeletal malformations, intrauterine growth retardation and embryoletality).

In view of these findings, particular care should be taken when prescribing DOLOPROCT during pregnancy. The results of epidemiological studies are summarized in the "*Pregnancy and Lactation*" section.

- Genotoxicity and Carcinogenicity

*In vitro* and *in vivo* studies gave no relevant indication of 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 related to the therapeutic use of fluocortolone pivalate.

There is at present no suggestion that lidocaine might be mutagenic. However, there are signs that a metabolite of lidocaine, 2,6-xylidin, that occurs in rats 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 local tolerance of the skin and 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.

### ***Pregnancy and Lactation***

#### **Use in Pregnancy**

Pregnancy Category B3. (Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed).

Animal experimental studies with glucocorticosteroids have shown reproductive toxicity and teratogenicity.

A number of epidemiological studies suggest that there could possibly be 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 with the use of DOLOPROCT since systemic availability of topically applied glucocorticosteroids is very low.

As a general rule, topical preparations containing glucocorticosteroids should not be used during the first trimester of pregnancy. The clinical indication for treatment with DOLOPROCT must be carefully reviewed and the benefits weighed against the risks in pregnant and lactating women. In particular, application in large amounts or for prolonged periods must be avoided.

### **Use in Lactation**

The excretion of effective amounts of glucocorticoid into breast milk is improbable.

### ***Effect on the Ability to Drive and Use Machines***

No observed effects.

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## **Adverse Effects**

### DOLOPROCT Rectal Cream

The incidence of adverse effects was calculated from pooled clinical trial data involving 661 patients. Adverse effects only concern skin disorders in the anal region with burning as common ( $\geq 1\%$ ,  $< 10\%$ ) and irritation and allergic reactions as an uncommon adverse effect ( $\geq 0.1\%$ ,  $< 1\%$ ). Allergic reactions to any of the ingredients of the cream cannot be ruled out.

After prolonged therapy with DOLOPROCT (more than 4 weeks), there is a risk that the patient may develop local skin alterations, such as atrophy, striae or telangiectasis.

### DOLOPROCT Suppositories

The incidence of adverse effects was calculated from pooled clinical trial data involving 367 patients. Adverse effects only concern skin disorders in the anal region with burning as common ( $\geq 1\%$ ,  $< 10\%$ ) and irritation and allergic reactions as an uncommon adverse effect ( $\geq 0.1\%$ ,  $< 1\%$ ). Allergic reactions to any of the ingredients of the suppositories cannot be ruled out.

After prolonged therapy with DOLOPROCT (more than 4 weeks), there is a risk that the patient may develop local skin alterations, such as atrophy, striae or telangiectasis.

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## **Interactions**

DOLOPROCT should be given with caution to patients who are treated with antiarrhythmic medicines.

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## Overdosage

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According to results from acute toxicity studies with the active substances contained in DOLOPROCT (fluocortolone and lidocaine hydrochloride) no acute risk of intoxication is to be expected following single rectal or perianal administration of DOLOPROCT, even after inadvertent overdose.

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

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## Pharmaceutical Precautions

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### *DOLOPROCT rectal cream*

**Shelf life:** 3 years unopened

**Special precautions for storage:** Store below 30 °C

### *DOLOPROCT suppositories*

**Shelf life:** 4 years unopened

**Special precautions for storage:** Store below 30 °C

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## Medicine Classification

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Prescription Medicine

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## Package Quantities

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Tubes containing 30 g of cream

Packs containing 10 suppositories

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## Further Information

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### *List of Excipients*

Rectal cream: polysorbate 60, sorbitan stearate, cetostearyl alcohol, liquid paraffin, white soft paraffin, disodium edetate, sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, benzyl alcohol, purified water

Suppositories: Hard fat (Witepsol W 35).

### *Nature and Contents of the Container*

**Rectal Cream:** Tubes of pure aluminium, interior wall coated with epoxy resin, and with a polyester-based external coating, fold seal ring is made of polyamide based heat-sealable material. The screw cap is made of high-density polyethylene and a polypropylene nozzle.

**Suppositories:** Two blister packs of aluminium-foil laminated with low-density polyethylene containing 5 suppositories each.

### ***Instructions for Use/Handling***

Store all medicines properly and keep them out of reach of children.

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### **Name and Address**

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Distributed in New Zealand by:

CSLBiotherapies (New Zealand) Limited  
666 Great South Road  
Penrose, Auckland 6, New Zealand.  
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### **Date of Preparation**

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