

Product Monograph

Pr^rLOCACORTEN[®] VIOFORM[®] Eardrops

(flumethasone pivalate 0.02% - clioquinol 1%)

Topical Corticosteroid with Antibacterial - Antifungal Agent
for Aural Use

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Actions and Clinical Pharmacology

LOCACORTEN (flumethasone pivalate) is a moderately potent difluorinated glucocorticoid with anti-inflammatory, antipruritic, and vasoconstrictive properties. As it is a pivalate, its action is concentrated at the site of application. This local effect on diseased areas results in a prompt decrease in inflammation, exudation and itching.

VIOFORM (clioquinol), the antimicrobial component of LOCACORTEN VIOFORM Eardrops, is active against a broad spectrum of pathogenic microorganisms, including fungi (e.g. *Candida*, *Microsporum*, *Trichophyton*) and gram-positive bacteria (e.g. *Staphylococci*). Clioquinol has only a slight inhibitory effect on gram-negative bacteria. Clioquinol exerts a bacteriostatic rather than a bactericidal action.

The polyethylene glycol vehicle is inert, non-irritant and viscous. This vehicle softens the cerumen and ensures prolonged contact of the active ingredients with the surface of the ear canal.

Indications and Clinical Use

LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/clioquinol) are indicated for:

- Otitis externa.
- Otomycosis including that due to *Aspergillus niger*.

Contraindications

LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/cliquinol) are contraindicated in:

- Perforation of the eardrum (suspected or verified).
- Viral (e.g., chicken pox) or syphilitic skin infections; tuberculosis of the skin; skin eruptions following vaccination.
- Known hypersensitivity to flumethasone pivalate or to corticosteroids in general, to hydroxyquinolines, cliquinol, or other quinoline derivatives, iodine, as well as to any other components of LOCACORTEN VIOFORM Eardrops (**see Composition in Pharmaceutical Information section**).
- Application to the eye.
- Use in children under 2 years of age.

Warnings

Use in Pregnancy and Lactation:

The safety of LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/cliquinol) during pregnancy or lactation has not been established. Studies have shown that corticosteroids may induce fetal abnormalities in pregnant animals. The relevance of this finding to human use has not been elucidated. It is not known whether the active substances pass into breast milk when applied topically. Therefore, the potential benefit of LOCACORTEN VIOFORM Eardrops during pregnancy (particularly during the first three months) or lactation, should be weighed against possible hazard to the fetus or the nursing infant.

Precautions

Prior to beginning therapy, the eardrum should be checked by the physician. LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/cliquinol) should not be used if there is a risk that perforation of the eardrum may occur or has occurred.

Topical use of cliquinol-containing preparations may lead to a marked increase in protein-bound iodine (PBI) (**See Symptoms and Treatment of Overdosage**).

Provided the preparation is used as recommended unwanted systemic effects are unlikely to occur. On basic medical grounds, the possibility of a clinically important effect on adrenocortical function should nevertheless be borne in mind, particularly in pediatric use and in patients undergoing prolonged therapy.

If no improvement occurs within 1 week, therapy should be discontinued; the pathogens should then be identified and treated.

Patients should, as a general rule, be advised to inform subsequent physicians of the prior use of corticosteroids.

LOCACORTEN VIOFORM Eardrops should not be allowed to come into contact with the conjunctiva (**see Contraindications**).

LOCACORTEN VIOFORM may turn yellow when exposed to air and may cause staining of the skin, nails, hair or fabrics.

Interactions:

Topical use of clioquinol, as well as other iodine-containing compounds, may increase the amount of protein-bound iodine (PBI) in patients with normal thyroid function and therefore may interfere with some thyroid function tests (such as PBI, radioactive iodine and butanol-extractable iodine). These tests should not be performed within 1 month of LOCACORTEN VIOFORM Eardrops use. Other thyroid function tests, such as the T₃ resin sponge test or the T₄ determination, are unaffected by clioquinol.

The ferric chloride test for phenylketonuria may yield a false-positive result when clioquinol is present in the urine.

Adverse Reactions

Occasionally: signs of irritation such as burning sensation, itching or skin rash at the site of application; hypersensitivity reactions.

If an exacerbation or allergic type reaction occurs, treatment with LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/clioquinol) should be discontinued.

Symptoms and Treatment of Overdosage

Poisoning due to accidental ingestion is not expected since a bottle of LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/clioquinol) contains far less active ingredients than the upper safe limit of a single oral dose for either component.

Application of clioquinol-containing preparations to extensive or eroded areas of skin may lead to increased PBI values within 1 week. Elevated PBI values may also occur where relatively small areas of skin are treated for more than 1 week. If signs and symptoms resembling those of thyrotoxicosis occur, the preparation should be withdrawn at once.

Dosage and Administration

Thorough cleansing of the external ear is essential for successful treatment. If a copious and offensive discharge is present, the meatus may initially require gentle syringing. Thereafter the passage may be kept clean by wiping as necessary.

Two to three drops of LOCACORTEN VIOFORM Eardrops (flumethasone pivalate/clioquinol) should be instilled twice daily.

The solution may be warmed to body temperature prior to application by holding the bottle in the hands. Heating above body temperature should be avoided.

To ensure correct administration of the drug, the patient or another person should be instructed both on how to clean the outer ear and apply the eardrops. The patient should be either sitting or lying down with the treated ear turned upwards during application. This position should be maintained for 1-2 minutes following the application.

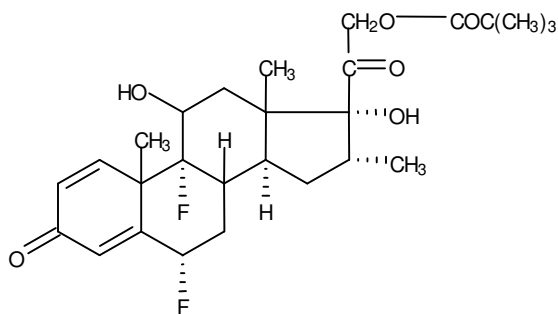
Free drainage of the ear encourages healing; however, in severe cases it may be desirable to pack the ear lightly with a gauze strip moistened with the solution, replacing this dressing as necessary, at least once every 24 hours.

To avoid contamination of the eardrops, contact of the dropper with any surface (including the ear) should be avoided.

Treatment should normally not exceed 10 days.

Pharmaceutical Information

Drug Substances



Flumethasone pivalate

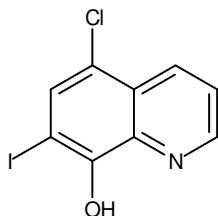
Chemical Name: 6a,9-difluoro-11b,17a-dihydroxy-16a-methyl-21-trimethylacetoxyl-1,4-pregnadiene-3,20-dione

Molecular Formula: $C_{27}H_{36}F_2O_6$

Molecular Weight: 494.6

Description: Virtually white, odorless, fine crystalline powder.

Solubility: Slightly soluble in methanol and ethanol, very slightly soluble in chloroform and methylene chloride, and is insoluble in carbon tetrachloride and isooctane.



Clioquinol

Chemical Name: 5-chloro-7-iodo-8-quinolinol

Molecular Formula: C₉H₅ClINO

Molecular Weight: 305.5

Description: Practically white to faintly yellowish powder.

Solubility: Freely soluble in pyridine, soluble in dimethylformamide and hot ethyl acetate, sparingly soluble in dioxane, slightly soluble in ethanol, practically insoluble in water.

Composition:

LOCACORTEN VIOFORM (flumethasone pivalate and clioquinol) Eardrops:

The solution contains the medicinal ingredients flumethasone pivalate and clioquinol, and the non-medicinal ingredient polyethylene glycol.

Stability and Storage Recommendations:

Protect from heat (store between 15-30°C) and light. LOCACORTEN VIOFORM Eardrops may turn yellow when exposed to air and may cause staining of the skin, nails, hair or fabrics.

Availability of Dosage Forms

^{Pr}LOCACORTEN[®] VIOFORM[®] (flumethasone pivalate and clioquinol) Eardrops:

Each 11 mL plastic dispenser of clear solution contains flumethasone pivalate (0.02%) and clioquinol (1%). Available in cartons containing one controlled-drop dispenser.

Information for the Consumer

Please read this information carefully before starting ^{Pr}LOCACORTEN[®] VIOFORM[®] Eardrops treatment.

What are LOCACORTEN VIOFORM Eardrops?

LOCACORTEN VIOFORM Eardrops contain flumethasone pivalate, which belongs to a group of medicines called corticosteroids, and clioquinol, an anti-infective agent.

What do LOCACORTEN VIOFORM Eardrops do?

LOCACORTEN VIOFORM Eardrops relieve the symptoms of ear infections, such as itching and redness. They also stop the growth of bacteria and fungi that cause ear infections.

Before using LOCACORTEN VIOFORM Eardrops

Be sure to tell your doctor:

- if you have ever had any unusual or allergic reactions to corticosteroids, iodine or iodine-containing preparations, cloquinol or hydroxyquinolines, or any other substances, including foods and dyes.
- if you have any problems with your ear, including a punctured eardrum.
- if you are pregnant or intend to become pregnant while using LOCACORTEN VIOFORM Eardrops, or if you are breast-feeding.

In these cases, your doctor will decide if you may use LOCACORTEN VIOFORM Eardrops.

How to use LOCACORTEN VIOFORM Eardrops

LOCACORTEN VIOFORM Eardrops must be used as directed by your doctor. Do not use more of it, do not use it more often, and do not use it for a longer period of time than your doctor has specified.

Some ear infections cause a discharge. As your ear must be clean for LOCACORTEN VIOFORM to effectively combat the infection, your doctor or pharmacist may show you how to clean your ears before instilling the drops. You may warm the eardrops to body temperature (but not warmer) before applying them to the ear by holding the bottle in your hands.

To instill the eardrops:

- 1) Lie down with the infected ear up and pull down gently on the ear lobe.
- 2) Instill the prescribed number of drops in the ear canal.
- 3) Gently push on the ear until the drops are evenly spread in the ear before sitting up.

To avoid contamination of the eardrops, do not let the dropper touch any surface (including the ear).

Keep the container tightly closed after use.

LOCACORTEN VIOFORM Eardrops are for external use only. Do not take by mouth.

What side effects can LOCACORTEN VIOFORM Eardrops have?

Like all medicines, LOCACORTEN VIOFORM Eardrops may cause some unwanted effects, in addition to their desired ones. If redness, burning, itching or other signs not present before using LOCACORTEN VIOFORM Eardrops occur, stop treatment, and consult your doctor or pharmacist.

If there is no improvement or if your ear infection becomes worse after you have used LOCACORTEN VIOFORM Eardrops for 1 week, see your doctor.

Other Precautions

Remember that LOCACORTEN VIOFORM Eardrops have been prescribed for your present medical problem only. Do not use it to treat other ear conditions without checking with your doctor first.

Do not use LOCACORTEN VIOFORM Eardrops in the eyes. If it gets in the eyes accidentally, flush them at once with plenty of water.

LOCACORTEN VIOFORM Eardrops may stain hair, skin, nails and fabric yellow.

LOCACORTEN VIOFORM Eardrops are not suitable for children under two years of age.

Storage:

Protect from heat (store between 15-30 °C) and light. LOCACORTEN VIOFORM Eardrops may turn yellow when exposed to air and may cause staining of the skin, nails, hair or fabrics.

Keep out of the reach of children.

Pharmacology

Locacorten

Flumethasone pivalate (LOCACORTEN) has marked local anti-inflammatory activity. Activity was quantified by comparing the degree of foreign body granuloma formation caused by implantation of a sterile cotton pellet versus a sterile cotton pellet impregnated with flumethasone pivalate or other corticoids, for 6 days under the skin of the back of male rats.

Flumethasone pivalate was more than 800 times as active as cortisol acetate, about 70 times as active as prednisolone trimethylacetate and about 10 times as active as dexamethasone trimethylacetate. In doses with an optimal local effect, flumethasone pivalate did not exert any remarkable effect on the contralateral control granuloma, and produced only insignificant changes of body weight, thymus and adrenal weight. This demonstrates the absence of systemic effects.

In normal male rats loaded orally with 20 mg/kg of a 0.85% NaCl solution, appreciable diuresis occurred within four hours after the administration of flumethasone pivalate in doses ≥ 0.02 mg/animal. Such an effect is typical for compounds of this type in rats.

Comparison to above data shows that the dose exerting a clear-cut inhibiting effect on the formation of foreign body granulomata is about 80 times smaller than that necessary to alter water and salt excretion in the same animal.

Vioform

The antifungal and antibacterial activities of clioquinol (VIOFORM) are shown in the following tables:

Table 1:

| Antifungal Spectrum | |
|----------------------------|--------------------------|
| Fungus | Effect of Vioform |
| Trichophyton Quinckeanum | ++ |
| Epidermophyta | ++ |
| Scopulariopsis brevicaulis | ++ |
| Candida albicans* | ++ |
| Aspergillus niger* | ++ |

Table 2:

| Antibacterial Spectrum | |
|-------------------------------|--------------------------|
| Bacterium | Effect of Vioform |
| Staphylococcus* | +++ |
| Streptococcus* | ++ |
| Ps. pyocyanea* | + |
| E. Coli* | ++ |
| B. anthracis | ++ |
| Kl. pneumonia | ++ |
| Pneumococcus* | +++ |
| Salmonella typhi | +++ |
| Salmonella paratyphi | +++ |
| Dysentery bacillus | +++ |
| Meningococcus | +++ |
| B. pseudodiphtheria | ++ |
| B. subtilis | ++ |
| Tubercle bacillus | ++ |

+++ = complete growth inhibition in appropriate concentration

++ = considerably decreased growth rate

+ = slight growth inhibition

* = organisms commonly occurring in ear infections

Toxicology

The LD₅₀ for flumethasone pivalate is >1000 mg/kg in the mouse, and >500 mg/kg in the rat. In dogs 0.01 mg/kg/day s.c. was well tolerated. This represents a dose 400-700 times greater than that needed to exert an optimal local effect.

In special human toxicity and absorption studies no systemic or pituitary - adrenal effects were noted. The only significant abnormalities found were elevated 17-ketosteroid levels and elevated serum PBI levels (LOCACORTEN VIOFORM Cream).

No systemic toxic effects due to absorption of LOCACORTEN VIOFORM Eardrops from the auditory canal were reported in clinical trials. However, transient reversible adrenocortical suppression occurred in three patients while using large amounts of 0.03% flumethasone pivalate cream, i.e., 90 g per day for 7 days over the entire body with about half the skin occluded at all times.

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