

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Xerese™ (acyclovir and hydrocortisone) cream 5%/1% safely and effectively. See full prescribing information for XERESE.

Xerese™ (acyclovir and hydrocortisone) cream 5%/1% for topical use
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

XERESE, a combination of acyclovir and hydrocortisone, is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older) (1).

DOSAGE AND ADMINISTRATION

Topically apply XERESE 5 times per day for 5 days. Therapy should be initiated as early as possible after the first signs and symptoms (i.e., during the prodrome or when lesions appear) (2).

DOSAGE FORMS AND STRENGTHS

Topical cream containing 5% acyclovir and 1% hydrocortisone (3).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Only for topical use of recurrent herpes labialis on the lips and around the mouth (5).

ADVERSE REACTIONS

The following most common adverse reactions (< 1%) were local skin reactions (6.2):

- Drying or flaking of the skin; burning or tingling, erythema; pigmentation changes.

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No drug interaction studies have been performed with XERESE.

USE IN SPECIFIC POPULATIONS

- Immunocompromised Patients: Benefit has not been adequately assessed (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 05/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 General
- 6 ADVERSE REACTIONS
 - 6.1 Overall Adverse Reaction Profile
 - 6.2 Adverse Reactions in Clinical Studies
- 7 DRUG INTERACTIONS
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Immunocompromised Subjects

- 10 OVERDOSAGE
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
 - 12.4 Microbiology
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
 - 14.1 Clinical Experience in Adults
 - 14.2 Clinical Experience in Pediatric Subjects
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
 - 17.1 General
 - 17.2 Instructions for Use

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XERESE is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older).

2 DOSAGE AND ADMINISTRATION

Topically apply XERESE 5 times per day for 5 days. Therapy should be initiated as early as possible after the first signs and symptoms (i.e., during the prodrome or when lesions appear).

For each dose, topically apply a quantity of XERESE sufficient to cover the affected area, including the outer margin. Avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection. For adolescents 12 years of age and older, the dosage is the same as in adults.

3 DOSAGE FORMS AND STRENGTHS

Each gram of XERESE contains 5% (w/w) acyclovir and 1% (w/w) hydrocortisone in an aqueous cream base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 General

XERESE is intended for cutaneous use only for herpes labialis of the lips and around the mouth. XERESE should not be used in the eye, inside the mouth or nose, or on the genitals.

There are other orofacial lesions, including bacterial and fungal infections, which may be difficult to distinguish from a cold sore. Patients should be encouraged to seek medical advice when a cold sore fails to heal within 2 weeks.

XERESE has a potential for irritation and contact sensitization [*see Adverse Reactions (6)*].

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

The safety data derived from XERESE clinical studies reflect exposure to XERESE in 1002 subjects with recurrent herpes labialis treated 5 times daily for 5 days. The majority of the adverse reactions were local skin reactions and occurred in the area of the application site.

6.2 Adverse Reactions in Clinical Studies

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical practice.

The majority of the adverse reactions were local and occurred in the area of the application site.

Skin and Subcutaneous Tissue Disorders

The following most common adverse reactions (< 1%) were local skin reactions, and occurred in the area of the application site:

- Drying or flaking of the skin; burning or tingling following application; erythema; pigmentation changes; application site reaction including signs and symptoms of inflammation.

Contact dermatitis following application has been observed when applied under occlusion in dermal safety studies. Where contact sensitivity tests have been conducted, the reactive substances were hydrocortisone or a component of the cream base.

A study enrolling 225 healthy adults was conducted to evaluate the contact sensitization potential of XERESE using repeat insult patch testing methodology. Of 205 evaluable subjects, one confirmed case (0.5%) of sensitization to hydrocortisone and 2 additional cases (1.0%) of possible sensitization to the XERESE base were identified. Additionally, one subject developed a contact allergy in the photosafety study to propylene glycol, one of the inactive ingredients of the cream base.

Dermal tolerance was assessed in a 21-day cumulative irritation study in 36 healthy subjects. XERESE, its cream base and Zovirax® (acyclovir) Cream 5% all showed a high and cumulative irritation potential under occlusive and semi-occlusive conditions.

Photoallergic potential and phototoxicity were assessed in two studies in 50 and 30 healthy volunteers, respectively. No photoallergic or phototoxicity potential was identified for XERESE.

7 DRUG INTERACTIONS

No drug interaction studies have been performed with XERESE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category B

Teratogenic Effects

Acyclovir was not teratogenic in the mouse, rabbit or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy between 1984 and 1999 followed 749 pregnancies in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximated that found in the general population. However, the size of the registry was insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Animal reproduction studies have not been conducted with XERESE. No studies have been performed in pregnant women. Systemic exposure of acyclovir and hydrocortisone following topical administration of XERESE is minimal.

8.3 Nursing Mothers

It is not known whether topically applied acyclovir or hydrocortisone is excreted in breast milk. Systemic exposure following topical administration of either drug is expected to be below detection limits. Because many drugs are excreted in human milk, caution should be exercised when XERESE is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric subjects less than 12 years of age have not been established.

8.5 Geriatric Use

In clinical studies, there were insufficient subjects above 65 years of age to reach a firm conclusion regarding safety and efficacy of XERESE in this group, although the available results were similar to lower age subjects.

8.6 Immunocompromised Subjects

Even though the safety of XERESE has been studied in immunocompromised subjects, data are insufficient to support use in this population. Immunocompromised subjects should be encouraged to consult a physician concerning the treatment of any infection.

Benefit has not been adequately assessed in immunocompromised patients. A randomized, double-blind study was conducted in 107 immunocompromised subjects with stable HIV infection and recurrent herpes labialis. Subjects had on average 3.7 episodes of herpes labialis in the previous 12 months. The median age was 30 years (range 19 to 64 years), 46% were female, and all Caucasian. Median CD4+ T-cell count at screening was 344/mm³ (range 100-500/mm³). Subjects were treated with XERESE or 5% acyclovir in XERESE vehicle. The primary objective was to exclude a doubling of the healing time in either treatment arm. The mean healing time for cold sores was similar between the two treatment groups: 6.6 days for XERESE and 6.9 days for 5% acyclovir in XERESE vehicle.

10 OVERDOSAGE

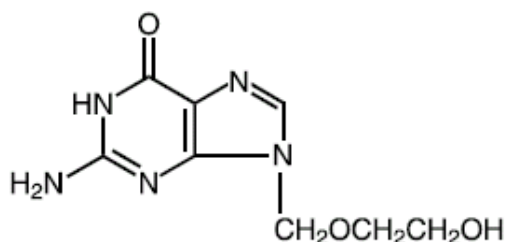
Overdosage by topical application of XERESE is unlikely because of minimal systemic exposure [see *Clinical Pharmacology- Pharmacokinetics* (12.3)].

11 DESCRIPTION

XERESE contains acyclovir, a synthetic nucleoside analogue active against herpes viruses, and hydrocortisone, an anti-inflammatory corticosteroid, combined in a cream for topical administration. Each gram of XERESE contains 5% (w/w) of acyclovir, 1% (w/w) of hydrocortisone and the following inactive ingredients: cetostearyl alcohol, mineral oil, Poloxamer 188, propylene glycol, isopropyl myristate, sodium lauryl sulfate, white petrolatum, citric acid, sodium hydroxide and water. Sodium hydroxide or hydrochloric acid may be added to adjust the pH to approximately pH 5.

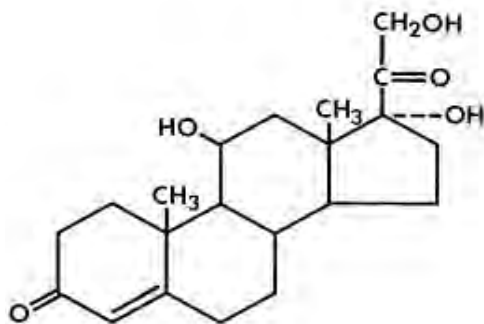
Acyclovir, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one, is a synthetic nucleoside analogue active against herpes viruses. The maximum solubility of acyclovir in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25. Its empirical formula is C₈H₁₁N₅O₃. The structural formula is provided in Figure 1:

Figure 1: Structural Formula of Acyclovir



Hydrocortisone, pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-(11(beta))-, is an anti-inflammatory corticosteroid. Its empirical formula is $C_{21}H_{30}O_5$. The structural formula is provided in Figure 2:

Figure 2: Structural Formula of Hydrocortisone



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acyclovir is an antiviral drug and hydrocortisone an anti-inflammatory drug. [see *Clinical Pharmacology - Microbiology* (12.4)].

12.3 Pharmacokinetics

The plasma concentrations of acyclovir and hydrocortisone were not measured following topical administration of XERESE on cold sores.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin and can have systemic side effects depending on both the potency of the corticosteroid and the surface area of application.

Inflammation and/or other disease processes in the skin that disrupt the skin barrier can increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. They are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

12.4 Microbiology

Mechanism of Action

Acyclovir is a synthetic purine nucleoside analogue with inhibitory activity against herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) in cell culture and *in vivo*.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In cell culture, acyclovir triphosphate stops replication of herpes viral DNA. This inhibition is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase.

Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex. It is used topically for its anti-inflammatory effects which suppress the clinical manifestations of the disease in a wide range of disorders where inflammation is a prominent feature.

Antiviral Activity

The quantitative relationship between the cell culture susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (EC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays on Vero cells, the median EC_{50} value of acyclovir against clinical herpes virus isolates (subjects receiving placebo) was 1.3 μ M (range: < 0.56 to 3.3 μ M).

Resistance

Resistance of HSV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV with reduced susceptibility to acyclovir have been recovered from immunocompromised subjects, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated from immunocompromised subjects thus far have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults.

The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Systemic exposure following topical administration of acyclovir is minimal. Results from previous studies of carcinogenesis, mutagenesis and fertility for acyclovir and hydrocortisone are not included in the full prescribing information for XERESE due to the minimal exposures that result from dermal application. Information on these studies following systemic exposure is available in the full prescribing information for acyclovir and hydrocortisone products approved for oral or parenteral administration. Dermal carcinogenicity studies have not been conducted.

14 CLINICAL STUDIES

14.1 Clinical Experience in Adults

In a double-blind, clinical study, 1443 subjects with recurrent labial herpes were randomized to receive XERESE, 5% acyclovir in XERESE vehicle or vehicle alone. Subjects had, on average, 5.6 episodes of herpes labialis in the previous 12 months. The median age was 44 years (range 18 to 80 years), 72% were female, and 91% were Caucasian. Subjects were instructed to initiate treatment within 1 hour of noticing signs or symptoms and continue treatment for 5 days, with application of study medication 5 times per day. Ulcerative cold sores occurred in 58% of the subjects treated with XERESE compared to 74% in subjects treated with vehicle and 65% in subjects treated with 5% acyclovir in XERESE vehicle. The mean time to skin normalization was approximately 1.6 days shorter in the subjects treated with XERESE compared to vehicle. Clinical signs in terms of size of the cold sore and symptoms such as tenderness were reduced with XERESE as compared to vehicle.

14.2 Clinical Experience in Pediatric Subjects

An open label safety study in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, 4.0 episodes of herpes labialis in the previous 12 months. The median age was 14 years (range 12 to 17 years); 50% were female and all were Caucasian. Therapy was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety and efficacy profile appeared similar to that observed in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

XERESE is supplied in plastic-laminated aluminum tubes containing 2 gm or 5 gm of XERESE. Each gram of XERESE contains 5% (w/w) acyclovir and 1% (w/w) hydrocortisone in an aqueous cream base.

NDC XXXXX-XXX-XXX: 2-gm tubes

NDC XXXXX-XXX-XXX: 5-gm tubes

Store at Controlled Room Temperature [20°-25°C (68°-77°F)]; excursions permitted to 15°-30°C (59°-86°F). Do not freeze.]

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

17.1 General

Patients should be informed that XERESE is not a cure for cold sores. Patients should be instructed that XERESE is intended for cutaneous use only for herpes labialis of the lips and around the mouth. Patients should be advised that XERESE should not be used in the eye, inside the mouth or nose, or on the genitals.

17.2 Instructions for Use

Patients should be advised to apply XERESE topically 5 times per day for 5 days. Patients should be instructed to topically apply a quantity of XERESE sufficient to cover the affected area, including the outer margin. Patients should be advised to avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection.

FDA-Approved Patient Labeling

PATIENT INFORMATION

Xerese™ (acyclovir and hydrocortisone) cream 5%/1%

XERESE is for cold sores on lips and around the mouth only. XERESE should not be used in eyes, mouth, nose or on genitals.

Read this Patient Information that comes with XERESE before you start using it and each time you get a refill. There may be new information. This patient leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is XERESE?

XERESE is a prescription medicine used in people ages 12 and older to lessen the healing time of cold sores (herpes labialis) and lessen the chance of a cold sore becoming worse (ulcerating).

XERESE is not a cure for cold sores.

It is not known if XERESE is safe or works in children younger than 12 years old.

What should I tell my doctor before using XERESE?

Before you use XERESE, tell your doctor if you:

- have a weak immune system (become sick very easily). It is not known if XERESE will harm you.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if XERESE will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if XERESE is passed in your milk to your baby.

How should I use XERESE?

- Use XERESE exactly as directed by your doctor.
- Use XERESE early, at the first sign of a cold sore.
- Wash your hands before and after using XERESE.
- Clean and dry the skin before applying XERESE.
- Spread a thin layer of XERESE on the affected area.
- Do not rub the cold sore because it may spread to other areas around your mouth, or make your cold sore worse.
- Do not cover the cold sore or area around the cold sore with a bandage.
- Do not use other skin products (such as make-up, sun screen or lip balm) or other skin medicine on the cold sore or area around the cold sore.
- Do not bathe, shower or swim until 30 minutes after applying XERESE.
- Talk to your doctor if your cold sore is not better in 2 weeks.

What are the possible side effects of XERESE?

The most common side effects of XERESE are:

- drying or flaking of the skin
- tingling or burning after you apply XERESE
- redness of the skin
- changes in your skin color where the cream is applied (pigmentation changes)
- swelling where XERESE was applied
- bitter taste after you apply XERESE.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XERESE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store XERESE?

- Store at temperatures between 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F).
- Do not freeze XERESE.
- Keep the XERESE tube closed tightly.

Keep XERESE and all medicines out of the reach of children.

General Information about XERESE

Medicines are sometimes prescribed for conditions that are not mentioned in patient leaflets. Do not use XERESE for a condition for which it was not prescribed. Do not give XERESE to other people, even if they have the same symptoms you have. It may harm them.

This patient leaflet summarizes the most important information about XERESE. If you would like to know more information about XERESE, talk with your doctor. You can ask your doctor or pharmacist for additional information about XERESE that was written for healthcare professionals.

What are the ingredients of XERESE?

Active Ingredients: acyclovir and hydrocortisone

Inactive ingredients: cetostearyl alcohol, mineral oil, Poloxamer 188, propylene glycol, isopropyl myristate, sodium lauryl sulfate, white petrolatum, citric acid, sodium hydroxide and water.

Revised: 05/2010

Manufactured for:
Medivir AB
PO Box 1086
SE-141 22 Huddinge
SWEDEN

Manufactured by:
Contract Pharmaceuticals Limited
7600 Danbro Crescent
Mississauga, Ontario
CANADA L5N 6L6