

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XERESE safely and effectively. See full prescribing information for XERESE.

XERESE® (acyclovir and hydrocortisone) cream for topical use

Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

Indications and Usage (1) 01/2014
Dosage and Administration (2) 01/2014

INDICATIONS AND USAGE

XERESE, a combination of acyclovir, a herpes simplex virus nucleoside analog DNA polymerase inhibitor, and hydrocortisone, a corticosteroid, 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 children (6 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. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

- Drying or flaking of the skin; burning or tingling, erythema; pigmentation changes; application site reactions including signs and symptoms of inflammation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No drug interaction studies have been performed with XERESE. (7)

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: 01/2014

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XERESE, a combination of acyclovir, a herpes simplex virus nucleoside analog DNA polymerase inhibitor, and hydrocortisone, a corticosteroid, 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 children (6 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 children 6 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* (6.1)].

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Trials

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

The safety data derived from XERESE clinical trials reflect exposure to XERESE in 1056 subjects with recurrent herpes labialis treated 5 times daily for 5 days.

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

- 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 trials. Where contact sensitivity tests have been conducted, the reactive substances were hydrocortisone or a component of the cream base.

A trial 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 trial in 36 healthy subjects. XERESE, its cream base and Zovirax® (acyclovir) Cream 5% all showed a high and cumulative irritation potential under occlusive and semioclusive conditions.

Photoallergic potential and phototoxicity were assessed in two trials 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

Teratogenic Effects

Pregnancy Category B. 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 trials 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 trials 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 6 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 trial 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

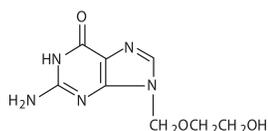
Overdosage by topical application of XERESE is unlikely because of minimal systemic exposure [see *Clinical Pharmacology* (12.3)].

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 have been added to adjust the pH to approximately pH 5.

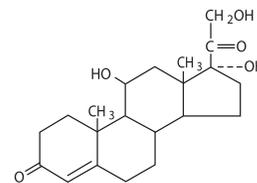
Acyclovir, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one, is a synthetic nucleoside analogue active against herpes viruses. The maximum solubility of acyclovir in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25. Its empirical formula is C₈H₁₁N₅O₃. The structural 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 C₂₁H₃₀O₅. 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 *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 (EC₅₀), vary greatly depending upon a number of factors. Using plaque-reduction assays on Vero cells, the median EC₅₀ value of acyclovir against clinical herpes virus isolates (subjects receiving placebo) was 1.3 μM (range: <0.56 to 3.3 μM).

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 Trial Experience in Adults

In a double-blind, clinical trial, 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 Trial Experience in Pediatric Subjects

An open label safety trial in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, 4 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. XERESE was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety profile of XERESE appeared similar to that observed in adults.

An open label safety trial in children with recurrent herpes labialis was conducted in 54 subjects, who averaged an episode of herpes labialis 2 months prior to trial entry. The mean age was 9 years (range 6 to 11 years); 57% were female and 90% were Caucasian. XERESE was applied using the same dosing regimen as in adolescents and adults and subjects were monitored for adverse events and select efficacy parameters. The safety profile of XERESE appeared similar to that observed in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 0187-5104-01: 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 (Patient Information)

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.

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.

PATIENT INFORMATION

XERESE® (sūr-eeze)

(acyclovir and hydrocortisone) Cream 5%/1%

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

What is XERESE?

- XERESE is a prescription medicine used in people 6 years of age and older to shorten the healing time of cold sores (herpes labialis) and lower 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 and effective in children less than 6 years of age.

What should I tell my healthcare provider before using XERESE?

Before using XERESE, tell your healthcare provider about all of your medical conditions, including if you:

- become sick very easily (have a weak immune system)
- are pregnant or plan to become pregnant. It is not known if XERESE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XERESE passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use XERESE?

- Use XERESE exactly as your healthcare provider tells you to use it.
- Use XERESE as soon as you have the first symptom of a cold sore such as itching, redness, burning or tingling or when the cold sore appears.
- Apply XERESE over the affected area, including the outer edge of the cold sore.
- Do not rub the cold sore because this may cause the cold sore to spread to other areas around your mouth, or make your cold sore worse.
- Do not cover the cold sore or the 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 the area around the cold sore.
- Tell your healthcare provider 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 skin reactions at the treatment site and may include:

- drying or flaking, tingling or burning after you apply XERESE, redness, changes in skin color where the cream is applied, and swelling.

These are not all the possible side effects of XERESE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XERESE?

- Store XERESE at room temperature between 68° to 77°F (20° to 25°C). Do not freeze XERESE.

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

General information about the safe and effective use of XERESE

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. 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 that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XERESE that is written for health professionals.

What are the ingredients in 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. May also contain hydrochloric acid.

Manufactured for:

Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807

Manufactured by:

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7600 Danbro Crescent
Mississauga, Ontario
Canada L5N 6L6

Produced under license: MEDA Pharma SARL, Luxembourg, by Valeant International Bermuda



For more information call 1-800-321-4576.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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