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

**INDICATIONS AND USAGE**

XERESE, a combination of acyclovir, a herpes simplex virus deoxynucleoside 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)

Cream: 50 mg (equivalent to 5%, w/w) acyclovir and 10 mg (equivalent to 1%, w/w) hydrocortisone. (3)

**ADVERSE REACTIONS**

Adverse Reactions (6.1)

XERESE has a potential for irritation and contact sensitization [see Advice when a cold sore fails to heal within 2 weeks.

There are other orofacial lesions, including bacterial and fungal infections, which may be treated with topical application of over-the-counter (OTC) products. See full prescribing information for XERESE.

**WARNINGS AND PRECAUTIONS**

None. (4)

**CONTRAINDICATIONS**

None.

**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: 12/2019
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from multiple large observational studies have not established an association with the use of topical acyclovir or low and medium potency topical corticosteroids (including hydrocortisone) during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available studies have methodological limitations including whether women who filled a prescription actually took the medication, non-randomized design, retrospective data collection, and the inability to control for confounders such as underlying maternal disease and use of concomitant medications.

8.2 Lactation

Risk Summary

There are no data on the presence of acyclovir or hydrocortisone in human milk following topical administration. There are no data on the effects of acyclovir or hydrocortisone on the breastfed infant or on milk production. Systemic exposure following topical administration of either drug is expected to be minimal. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for XERESE and any potential adverse effects on the breastfed child from XERESE or from the underlying maternal condition.

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 50 mg (equivalent to 5%, w/w) of acyclovir, 10 mg (equivalent to 1%, w/w) of hydrocortisone and the following inactive ingredients: cetostearyl alcohol, citric acid monohydrate, isopropyl myristate, mineral oil, Poloxamer 188, propylene glycol, purified water, USP , sodium hydroxide, sodium lauryl sulfate, and white petrolatum. Sodium hydroxide or hydrochloric acid may have been added to adjust the pH to approximately pH 5.

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 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acyclovir is an antiviral drug active against α-herpesviruses and hydrocortisone is an anti-inflammatory drug [see Microbiology (12.4)].

12.3 Pharmacokinetics

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12.4 Microbiology

Mechanism of Action

Acyclovir is a synthetic purine deoxynucleoside analogue with inhibitory activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) DNA polymerases. It inhibits HSV-1 and HSV-2 replication in cell culture and in vivo.

The inhibitory activity of acyclovir is selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV. This viral enzyme converts acyclovir into acyclovir monophosphate, a deoxynucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In biochemical assays, acyclovir triphosphate inhibits replication of α-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 susceptibility of herpes viruses to antivirals in cell culture 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 value), vary greatly depending upon a number of factors. Using plaque-reduction assays on vero cells, the EC50 value of acyclovir against herpes virus isolates ranged from 0.09 to 60 µM (0.02 to 13.5 µg/mL) for HSV-1 and from 0.04 to 44 µM (0.01 to 9.9 µg/mL) for HSV-2.

Resistance

In Cell Culture

Acyclovir-resistant HSV-1 and HSV-2 strains were isolated in cell culture. Acyclovir-resistant HSV resulted from mutations in the viral thymidine kinase (TK; pUL23) and DNA polymerase (POL; pUL30) genes. Frameshifts were commonly isolated and result in premature truncation of the HSV TK product with consequent decreased susceptibility to acyclovir. Mutations in the viral TK gene may lead to complete loss of TK activity (TK negative), reduced levels of TK activity (TK partial), or alteration in the ability of viral TK to phosphorylate the drug without an equivalent loss in the ability to phosphorylate thymidine (TK altered). In cell culture the following resistance-associated substitutions in TK of HSV-1 and HSV-2 were observed (Table 1).

Table 1: Summary of Acyclovir (ACV) Resistance-associated Amino Acid Substitutions in Cell Culture

<table>
<thead>
<tr>
<th>Virus</th>
<th>TK Substitution</th>
<th>POL Substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td>L69P, C172R, T288M</td>
<td></td>
</tr>
<tr>
<td>HSV-2</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Structural Formula of Hydrocortisone

![Figure 2: Structural Formula of Hydrocortisone](image-url)

Hydrocortisone, pregn-4-one-3,20-dione, 11,17,21-trihydroxy- (11β), is an anti-inflammatory corticosteroid. Its empirical formula is C21H30O5. The structural formula is provided in Figure 2:

![Figure 1: Structural Formula of Acyclovir](image-url)
In HSV-Infected Patients
Clinical HSV-1 and HSV-2 isolates obtained from patients who failed treatment for their α-herpesvirus infections were evaluated for genotypic changes in the TK and POL genes and for phenotypic resistance to acyclovir (Table 2). HSV isolates with filamentous mutations and resistance-associated substitutions in TK and POL were identified. The listing of substitutions in HSV TK and POL leading to decreased susceptibility to acyclovir is not all inclusive and additional changes will likely be identified in HSV variants isolated from patients who fail acyclovir-containing regimens. The possibility of viral resistance to acyclovir should be considered in patients who fail to respond or experience recurrent viral shedding during therapy.

Table 2: Summary of ACV Resistance-associated Amino Acid Substitutions Observed in Treated Patients

<table>
<thead>
<tr>
<th>HSV-1</th>
<th>TK</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td>TK</td>
</tr>
<tr>
<td>HSV-1</td>
<td>POL</td>
</tr>
<tr>
<td>HSV-2</td>
<td>POL</td>
</tr>
</tbody>
</table>

Note: Additional substitutions to acyclovir resistance may exist.

Cross-resistance has been observed among HSV isolates carrying filamentous mutations and resistance-associated substitutions, which confer reduced susceptibility to penciclovir (PCV), famciclovir (FCV), and foscarnet (FOS) (Table 3).

Table 3: Summary of Amino Acid Substitutions Conferring Cross-Resistance to PCV, FCV or FOS

<table>
<thead>
<tr>
<th>Cross-resistant to PCV/FCV</th>
<th>HSV-1</th>
<th>TK</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td>POL</td>
<td></td>
</tr>
<tr>
<td>A657T, D672N, V715G, A719V, S724N, E798K, N815S, G841S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-1</td>
<td>POL</td>
<td></td>
</tr>
<tr>
<td>G39E, R51W, Y53N, R177W, R221H, T288M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-2</td>
<td>TK</td>
<td></td>
</tr>
<tr>
<td>HSV-2</td>
<td>POL</td>
<td></td>
</tr>
</tbody>
</table>

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, 1,443 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.

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.

15 HOW SUPPLIED/STORAGE AND HANDLING
XERESE is supplied in a plastic-laminated aluminum tube containing 5 g of XERESE. Each gram of XERESE contains 50 mg (equal to 5%, w/w) acyclovir and 10 mg (equal to 1%, w/w) hydrocortisone in an aqueous cream base.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the 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
Advise patients to apply XERESE topically 5 times per day for 5 days. Instruct patients to topically apply a quantity of XERESE sufficient to cover the affected area, including the outer margin. Advise patients to avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection.

Manufactured for:
Bausch Health US, LLC
Bridgewater, NJ 08807 USA

By:
Bausch Health Companies Inc.
Laval, Quebec H7L 4A8, Canada

Product under license from Meda Pharma S.A.R.L., Luxembourg by Bausch Health Ireland Limited, Dublin, Ireland

U.S. Patent Number: 7,223,387

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**PATIENT INFORMATION**

**XERESE®** (sûr-euze)  
(acyclovir and hydrocortisone) Cream 5%/1%

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### Important information: XERESE is for use on cold sores on the lips and around the mouth only.

XERESE should not be used in your 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. Talk with your healthcare provider about the best way to feed your baby if you use XERESE.

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 healthcare professionals.

### What are the ingredients in XERESE?

**Active ingredients:** acyclovir and hydrocortisone

**Inactive ingredients:** cetostearyl alcohol, citric acid monohydrate, isopropyl myristate, mineral oil, Poloxamer 188, propylene glycol, purified water, USP, sodium hydroxide, sodium lauryl sulfate, and white petrolatum. May also contain hydrochloric acid.

**Manufactured for:** Bausch Health US, LLC, Bridgewater, NJ 08807 USA

**By:** Bausch Health Companies Inc., Laval, Quebec H7L 4A8, Canada

Product under license from Meda Pharma S.A.R.L., Luxembourg by Bausch Health Ireland Limited, Dublin, Ireland

U.S. Patent Number: 7,223,387

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

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

Revised: 12/2019

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