

PRODUCT MONOGRAPH

**ABREVA<sup>®</sup>**

**Docosanol Cream, 10%**

***Viral Entry Blocking Agent***

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# ABREVA®

## Docosanol Cream 10%

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Topical	Docosanol Cream, 10%	sucrose stearate (and) sucrose distearate, light mineral oil, propylene glycol, benzyl alcohol and purified water.

#### INDICATIONS AND CLINICAL USE

ABREVA® (docosanol cream 10%) is indicated for the treatment of acute episodes of recurrent oral-facial herpes simplex (fever blisters or cold sores) in adults.

Abreva® shortens healing time and the duration of cold sore symptoms including pain, burning, tingling and itching.

Abreva® soothes on contact.

#### Patient Subsets:

##### Geriatric Use

In 39 patients 65 years of age, the adverse events profile was comparable to that of younger patients.

##### Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Abreva has not been studied in children under 12 years of age. A doctor should be consulted before use in this patient population.

##### Pregnancy

###### **Teratogenic Effects:**

No evidence of impaired fertility or harm to the fetus due to docosanol administered in oral doses of 10, 500, 1000, or 2000 mg/kg/day was observed in reproduction studies performed in rat and rabbits. Based on the lack of absorption of topically applied docosanol, these tested doses are a thousand-fold higher than the human dose. However no adequate and well-controlled studies were conducted in pregnant humans. Because animal reproduction studies are not always predictive of human response, ABREVA® should be used during pregnancy only if clearly needed.

##### Nursing Mothers

It is not known whether docosanol is excreted in human milk. Caution should be exercised when ABREVA is administered to a nursing woman and/or consult your doctor before breast-feeding.

**CONTRAINDICATIONS**

ABREVA® (docosanol cream 10%) is contraindicated in patients with known hypersensitivity to docosanol or any of the components in the ABREVA® formulation. For a complete listing of the product composition, please refer to the section on Dosage Forms, Composition and Packaging.

**WARNINGS AND PRECAUTIONS**

ABREVA® should only be used to treat cold sores on the lips and face. Ophthalmic, penile, and vaginal irritation studies in rabbits demonstrate minimal irritation when ABREVA® is placed on these tissues. Care should be taken to avoid application in or near the eyes since it may cause irritation; if contact occurs, rinse thoroughly with water. If excessive skin irritation develops or increases, discontinue use and consult a doctor. It should not be taken orally. Docosanol must not be applied directly inside the mouth. The product must not be shared with anyone as this may spread infection. If the cold sore gets worse or is not healed within 10 days, a doctor should be consulted. Docosanol should be kept out of the reach of children.

**ADVERSE REACTIONS****Clinical Trial Data**

In double-blind clinical trials for the treatment of recurrent oral-facial herpes simplex, a total of 1008 patients were treated with docosanol cream 10% and 989 with placebo. The most frequently reported adverse event was headache, which occurred in 10.4% of the patients treated with docosanol cream 10% and 10.7% of the patients treated with placebo. One or more local adverse reactions were reported by 4.4% of patients treated with ABREVA® and 3.2% of placebo treated patients (Table 1). No evidence of contact sensitization or photoallergy was observed.

**Table 1: Local Adverse Reactions Reported in North American Phase 2/3 Clinical Trials**

Description	ABREVA®(N=1008) %	Placebo (N=989) %
Application site reaction	2.9	2.3
Rash	0.5	0.8
Pruritis	0.4	0.2
Dry skin	0.4	0.2
Acne	0.3	0.0

**Post Marketing Data**

As these reactions are reported voluntarily from a population of uncertain size, the frequency of these events is unknown but likely to be rare. Adverse reactions may include application site reactions (e.g. tingling or burning sensation), and hypersensitivity reactions (e.g. rash, pruritus and angioedema). These reactions are generally mild.

**DRUG INTERACTIONS**

Interactions with other drugs, foods and herbal products have not been established.

**DOSAGE AND ADMINISTRATION**

ABREVA® (docosanol cream 10%) should be applied topically 5 times/day and continued until the lesion is healed up to a maximum of 10 days. Begin treatment as soon as possible, preferably at the prodrome or erythema stage. Treatment is most effective if applied at the first symptoms (pain, itching, burning or tingling) or sign, (redness), prior to the formation of a papule (bump) or a blister.

## **OVERDOSAGE**

Adverse reactions related to overdosage by topical application or ingestion of docosanol cream 10% is considered unlikely due to limited transcutaneous and systemic absorption.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The predominant mechanism for the anti-HSV activity of docosanol appears to be inhibition of fusion between the plasma membrane and the HSV envelope. This blocks viral entry into the cell and subsequent viral replication.

This mechanism of action explains the effectiveness of docosanol against all tested lipid-enveloped viruses that employ fusion as the sole or major means of entry into the cell. This is in contrast to the mode of action of currently available antiviral agents that target a single viral protein.

### **Pharmacokinetics**

Under conditions reflecting normal clinical use of ABREVA® (docosanol cream 10%), the active ingredient could not be quantified (LOQ=10 ng/mL) in the plasma of treated patients. Ten women with active oral-facial herpes simplex lesions were treated with ABREVA™, applied as a single dose (Day 1), and as multiple topical doses (five times daily, Days 2 and 3). Blood samples were withdrawn at intervals up to 24 hours after treatment and analyzed for docosanol. Of the 209 plasma samples analyzed, the docosanol level was below the limit of quantitation in 208 and exactly 10 ng/mL in the other.

*n*-Docosanoic acid, the major metabolite of docosanol, is an endogenous component of cell membranes in man, particularly in erythrocytes, brain, nerve myelin sheath, lung and kidney.

## **STORAGE AND STABILITY**

Store between 15°C - 25°C. Do not freeze.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

ABREVA® (docosanol cream 10%) is available in a 2g tube or a pump.

Each gram of cream contains: docosanol 100 mg (10%).

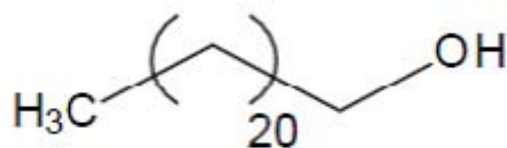
Non-medicinal ingredients: sucrose stearate (and) sucrose distearate, light mineral oil, propylene glycol, benzyl alcohol and purified water.

**PART II: SCIENTIFIC INFORMATION****PHARMACEUTICAL INFORMATION****Drug Substance**

Proper name: Behenyl Alcohol

Chemical name: *n*-DocosanolMolecular formula and molecular mass: C<sub>22</sub>H<sub>46</sub>O, 326.61

Structural formula:



Physicochemical properties:

*Physical Form:* A white, waxy solid*Melting Point:* 70°C to 72°C*Partition Coefficient:* *n*-Octanol-water partition coefficient is 12.1 (log P) (HPLC).*Hygroscopicity:* Docosanol is not hygroscopic.*Solubility at 25°C:*

Solvent	mg docosanol/mL
<i>n</i> -Hexane	3.4
Methanol	1.9
95% Ethanol	3.7
Chloroform	54.0
1-Octanol	15.8
Water	Insoluble

**CLINICAL TRIALS**

ABREVA® was studied in two pivotal clinic-initiated, double-blind, placebo-controlled multicentre trials for the treatment of recurrent oral-facial herpes simplex. Otherwise healthy adults were randomized to either ABREVA® or placebo treatments. First dose of therapy was made by the subject in clinic at the beginning of an episode before the development of a papule or blister. The study cream was applied topically 5 times/day until healing occurred or for a maximum of 10 days.

Patients presented to clinic for assessment twice daily for the first seven days. Patients whose episodes did not abort or heal within seven days were instructed to return once daily on Days 8 to 10. At each study visit the patient was evaluated as to whether the episode had aborted, progressed to a later stage, or healed.

The primary efficacy endpoint, time to healing, was defined as the time from initiation of therapy to complete resolution of all local signs and symptoms. All episodes began at treatment initiation and ended with the loss of crust for episodes that progressed beyond the papule stage, or at the aborted stage for episodes that did not progress beyond papule. The episode baseline and endpoint were determined by the clinician.

Twenty-one U.S. sites randomized 743 patients, 373 to ABREVA® and 370 to placebo. The sites were geographically diverse and included a variety of settings, including private practices, public health facilities, and universities. No single center enrolled more than 12% of the total combined study population. The Intent-To-Treat (ITT) analysis population included all randomized patients who had at least one post-baseline clinical assessment. Six patients (three in each treatment group) were excluded because they did not have any post-baseline clinical assessments; the ITT analysis included 370 patients on ABREVA and 367 on placebo.

In addition to the six patients excluded from the ITT population, an additional 19 patients (eight ABREVA and eleven placebo) were lost to follow-up or otherwise not compliant with the protocol and therefore excluded from the efficacy evaluable (EE) population (362 on ABREVA and 356 on placebo). The results were similar for both the ITT and the EE populations.

When the two studies were analyzed separately, the results were consistent with the results of the combined analysis. In the combined analysis of the pivotal clinical trials, the median time to healing of a recurrent oral-facial herpes simplex episode in the 370 ABREVA®-treated patients (4.1 days) was 0.7 days shorter than that observed in the 367 placebo-treated patients (4.8 days). The difference between the groups in median healing time was statistically significant ( $p=0.0076$ ), using the Generalized Wilcoxon analysis.

When the two studies were analyzed separately, the results were consistent with the results of the combined analysis, and also showed that the time to complete healing was statistically significantly shorter in the ABREVA group than in the placebo group.

The time to complete healing in both the ABREVA® and placebo groups was notably shorter than both the 6.2 – 8.3 days average healing time cited in the literature for untreated episodes and the average of 9 days cited as the historical episode duration by the study patients.

In addition to the positive treatment effect for the primary efficacy parameter in the trials, ABREVA® also demonstrated statistically significant reductions in duration of the important oral-facial herpes simplex associated symptoms of pain and/or burning, itching or tingling when compared to placebo ( $p=0.002$ ).

The clinical studies also showed that aborted episodes occurred in 40% (147/370) of patients in the ABREVA group as compared to 34% (125/367) of patients in the placebo group ( $p=0.109$ ).

## DETAILED PHARMACOLOGY

**Animal Pharmacology:** In two different mouse models, docosanol demonstrated anti-inflammatory activity. Topically administered docosanol caused a significant reduction in lesion severity in a phenol-induced contact dermatitis (chemical burn) model. In the collagen induced arthritis model, administration of docosanol intravenously and subcutaneously significantly lessened arthritic clinical signs and hastened complete remission of the disease.

**Drug Resistance:** The emergence of HSV strains resistant to the antiviral effects of docosanol is unlikely based on the drug's mechanism of action. Docosanol does not act directly on the virus rather, it appears to modulate the host cell to inhibit fusion of the viral envelope with the plasma membrane and prevent entry of the virus into the cell. Therefore, in contrast to the mode of action of other nucleoside antiviral agents which interact with the virus, the emergence of drug-resistant virus is improbable with docosanol. Furthermore, it has been demonstrated *in vitro* that docosanol inhibits cell entry of nucleoside-resistant HSV.

## MICROBIOLOGY

Cells treated with docosanol resist infection by all tested lipid-enveloped viruses entering cells via fusion with the plasma membrane, including HSV-1 and HSV-2, although the drug has no direct viricidal activity. Non-enveloped viruses are not inhibited.

**Antiviral Activity *In Vitro* and *In Vivo*:** Docosanol exhibits antiviral activity *in vitro* against many lipid-enveloped viruses, including HSV-1, HSV-2, VZV, CMV, HHV-6, RSV, influenza A, and HIV-1. Detailed HSV studies reveal that following cellular metabolism, docosanol interferes with one or more steps of viral entry, although docosanol does not affect binding of HSV to target cells. HSV virions bound to target cell receptors remain on the cell surface for a prolonged time. Studies using fluorescently labeled HSV confirm that fusion of the viral envelope with the cell membrane is inhibited. Consistent with this inhibition of viral entry, virion migration to the nucleus is significantly inhibited and there is a reduced expression of viral gene products in cells treated with docosanol. Sensitivity test results, expressed as the dose of drug required to inhibit growth of the virus by 50% (ID<sub>50</sub>) in cell culture are shown in Table 2. These test results are known to vary depending upon a number of factors, e.g. assay protocol, physical-chemical properties of the test compound, and viral load.

**Table 2: *In Vitro* Antiviral Activity of Docosanol**

<b>Virus Type (Strain)</b>	<b>Cell Type</b>	<b>ID<sub>50</sub>* (mM)</b>	<b>Method of Assay</b>
HSV-1 (MacIntyre)	Vero	6-9	Plaque reduction
HSV-1 (MacIntyre)	Human fetal foreskin	6-9	Plaque reduction
HSV-1 (MacIntyre) acyclovir-resistant	Vero	6-9	Plaque reduction
HSV-1 (KOS)	Vero	9	Cytopathic effect (microscopic examination)
HSV-1 (KOS)	Vero	12	Neutral red
HSV-2 (MS)	Vero	6-9	Plaque reduction
HSV-2 (MS)	Human fetal foreskin	6-9	Plaque reduction
HSV-2 (MS)	MDBK	15-24	Plaque reduction
HSV-2 (MS) acyclovir-resistant	Vero	6-9	Plaque reduction
HSV (oral clinical isolate)	Vero	15	Plaque reduction
HSV (genital clinical isolate)	Human fetal foreskin	9	Plaque reduction
VZV	MRC-5	3	Plaque reduction
CMV	MRC-5	6-9	Plaque reduction
HHV-6	PHA-stimulated human PPBMCs	6	p41 ELISA

Reported values are considerably higher than the actual bioactive concentrations in the cell culture due to the aqueous insolubility of docosanol.

*In vivo* antiviral blocking activity has been demonstrated against HSV-1 and HSV-2 in hairless and Hartley guinea pig models.

## **TOXICOLOGY**

Thirty-five GLP toxicology studies have been conducted to examine for possible toxicity of docosanol or ABREVA® (docosanol cream 10%) in a number of animal species. These included a single dose oral study in the rat, a single dose topical study in the rat, and two single dose topical studies in the rabbit. Repeat dose toxicology studies included topical studies with docosanol containing creams in the mouse (one study) and in the rabbit (two studies). Repeat oral dose toxicology studies were conducted in the rat (one preliminary and one main study) and dog (one preliminary and one main study). In these studies systemic exposure to docosanol was confirmed with toxicokinetic assessments. Local tolerance and special toxicity were assessed in 11 studies in guinea pigs and rabbits which served to assess contact sensitization, allergic potential, phototoxicity, photosensitivity, potential for



eye irritation, potential for vaginal irritation, and the potential for penile irritation. Nine reproductive toxicology studies were conducted in the rat and rabbit. Four mutagenicity studies were conducted.

The results of these studies demonstrated that docosanol is well tolerated dermally and exhibits no toxicity following oral ingestion. No significant adverse reactions to the intact or abraded skin were noted in mice or rabbits, and no contact hypersensitivity, phototoxicity, or photosensitivity was noted in guinea pigs. Oral ingestion resulted in no significant toxicity at single doses up to 2000 mg/kg in rat or repeat doses ranging up to 1000-2000 mg/kg/day for 26 weeks for rat and dog. No drug associated reproductive toxicity was observed at doses up to 1000 and 2000 mg/kg/day for rat and rabbit, respectively. The mutagenicity studies conducted *in vitro* and *in vivo* provided no evidence of mutagenic potential.

The findings from the collective studies related to treatment with docosanol or with docosanol 10% cream were limited to minimal irritation following topical administration to the skin or vaginal tissue of rabbits, pale feces in dogs and rabbits following high oral doses of docosanol (greater than 500 mg/kg/day), and minimal irritation when instilled into rabbit eyes or as assessed in the BECAM assay (although the mildly irritant properties observed would allow its classification as a non-irritant according to EEC criteria).

**Carcinogenesis:** Dermal and gastrointestinal absorption of docosanol from ABREVA® is limited, and orally absorbed docosanol is rapidly oxidized, evidently by normal metabolic processes. Both docosanol and its major active metabolite, *n*-docosanoic acid, are endogenous components of human tissues, docosanol being present in skin and secretions and *n*-docosanoic acid occurring in cell membranes, particularly in erythrocytes, brain, nerve myelin sheath, lung and kidney. Both compounds are present in many common foods and are virtually unavoidable in the diet. Estimated dietary intakes far exceed levels achievable from topical administration of ABREVA® during treatment of recurrent herpes simplex labialis. Based on these factors, and the lack of any evidence of mutagenicity from a battery of standard tests, the regulatory requirement for carcinogenicity studies was waived.

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## PART III: CONSUMER INFORMATION

### ABREVA® Docosanol Cream 10%

**For the Treatment of Recurrent Cold Sores  
The Only Docosanol-Containing Non-Prescription  
Medicine Which Inhibits Entry of the Cold Sore Virus  
into Surrounding Cells**

*For External Use Only*

This leaflet is part III of a three-part "Product Monograph" published when ABREVA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Abreva®. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What are cold sores (fever blisters)?

Cold sores on the face or mouth, is a common condition also known as fever blisters or recurrent herpes labialis. Cold sores are caused by a re-infection of the cells by the herpes simplex virus which remains dormant in your body after your initial infection. While there is no cure for the virus that causes cold sores, the severity and duration of the episodes may be reduced by appropriate treatment.

#### What the medication is used for:

ABREVA® is a medication for the treatment of cold sores in adults and children 12 years and over. It shortens healing time and the duration of cold sore symptoms including pain, burning, tingling and itching.

#### How does Abreva work:

ABREVA® contains docosanol, a substance which blocks the ability of the cold sore virus to enter your skin cells, limiting its ability to spread to surrounding cells. The average time to heal a cold sore with Abreva® is 4.1 days.

#### When it should not be used:

ABREVA® should not be used by patients with known allergies to docosanol or any other ingredients in this product. Refer to the non-medicinal ingredients part of this insert.

#### What the medicinal ingredient is:

Docosanol Cream 10%

#### Non-medicinal ingredients:

(alpha) benzyl alcohol, light mineral oil, propylene glycol, sucrose distearate, sucrose stearate, water.

#### What dosage forms it comes in:

ABREVA® is a white, odorless, non-staining, non-greasy cream for topical administration only. ABREVA® is available in a 2g tube or pump.

## WARNINGS AND PRECAUTIONS

### Warnings and Precautions

ABREVA® should only be used to treat cold sores on the lips and face. When using this product, apply only to affected areas. Avoid applying inside the mouth. Care should be taken to avoid application in or near the eyes since it may cause irritation; if contact occurs, rinse thoroughly with water. If excessive skin irritation develops or increases, discontinue use and consult a doctor. It should not be taken orally.

**BEFORE you use ABREVA® talk to your doctor or pharmacist for:**

- **Use of ABREVA® in pregnancy and breast-feeding**  
ABREVA® is not recommended for use during pregnancy or while breast-feeding unless advised by a physician.
- **Use in children**

ABREVA® has not been studied in children. Do not use in children under 12 years of age unless advised by your doctor.

### PROPER USE OF THIS MEDICATION

#### Usual dose:

#### **How to use Abreva®**

Wash your hands and then apply the required amount of ABREVA® to the tip of your finger or cotton swab. ABREVA® should then be rubbed in gently, but completely, into the area around your cold sore. Repeat this **5** times per day until the lesion is healed, up to a maximum of 10 days. Begin treating **at the first symptoms or signs of an episode** (itching, burning, tingling or redness), because **early treatment is important for best results**.

**Tube:** Wash your hands again and avoid contaminating the tip of the tube after applying the cream to the cold sore. Place cap back on tube.

**Pump:** Remove cap and press pump firmly. When first used, expect to press pump completely about 6-8 times to obtain the first dose. Place cap back on pump after each use. Wash hands after applying the cream.

Stop use and ask a doctor if your cold sore gets worse or the cold sore is not healed within 10 days.

To avoid spreading infection, do not share this medicine.

Cosmetics may be applied after ABREVA® is rubbed in, using a separate applicator to avoid spreading the infection.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In clinical trials for the treatment of cold sores, side effects were generally mild and occurred with the same frequency in patients treated with non-medicated cream (placebo). The most frequently reported adverse event was headache. Local adverse effects included a reaction at the site of application, rash, itching, dry skin and acne. Stop taking this medicine and contact your doctor if you experience an allergic reaction (e.g. rash, itchy skin). Report any bothersome or unusual symptoms to your doctor.

### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

Fax toll-free to 1-866-678-6789, or

Mail to:

Canada Vigilance Program

Health Canada

Postal Locator 0701D

Ottawa, Ontario

K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## HOW TO STORE IT

Keep out of the reach of children.

Store between 15° - 25°C. Do not freeze.

## INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: [www.abreva.ca](http://www.abreva.ca) or by contacting the sponsor, GlaxoSmithKline Consumer Healthcare Inc., at: 1-888-7-abreva

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