Safety Data Sheet
Acyclovir Cream, 5%
Strength: 5 % **Pack Size:** 5 gm **NDC** 72578-101-05 **Revision No.:** 01

Emergency Overview

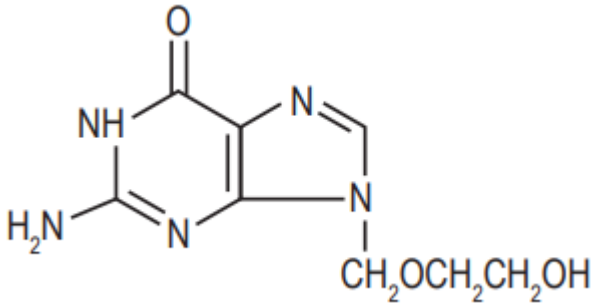
Acyclovir cream, 5% is a herpes simplex virus (HSV) deoxynucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.

Section 1 : Identification

Product Name: **Acyclovir Cream, 5%**

Formula: $C_8 H_{11}N_5O_3$

Chemical Name: 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one



Molecular Weight: 225.20 g/mol

Description: Acyclovir is a synthetic deoxynucleoside analogue active against herpes viruses. Acyclovir cream 5% is a formulation for topical administration.

Dosage forms and strengths: Each gram of acyclovir cream contains 50 mg (equivalent to 5% w/w) of acyclovir.

Manufacturer / supplier identification

Company	Cadila Healthcare Ltd. Ahmedabad, India
Address	Cadila Healthcare, Ltd. Changodar (Topical Formulation facility) Plot No. 254, Opp. Laxmi Narayan Petrol Pump, N.H. 8A, Ahmedabad -382210 India
Contact for information	Tel.:+91 2717-616430 Fax: +91 2717-616430
Emergency Telephone No	Tel.:+91 2717-616401
Recommended use / Therapeutic Category	Acyclovir cream, 5% is a herpes simplex virus (HSV) deoxynucleoside analogue DNA polymerase inhibitor indicated for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults and adolescents 12 years of age and older.
Restriction on Use / Contraindications	Acyclovir cream is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation.

Section 2 : Hazard (s) Identification

Dose and Administration

Acyclovir cream should be applied 5 times per day for 4 days. Therapy should be initiated as early as possible following the onset of signs or symptoms of herpes labialis i.e., during the prodrome or when lesions appear.
For adolescents 12 years of age and older, the dosage is the same as in adults.

Adverse effects

Clinical trial experience:
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in clinical practice.
In five double-blind, placebo-controlled trials, 1,124 patients were treated with acyclovir cream and 1,161 with placebo (vehicle) cream. Local application site reactions were reported by 5% of patients receiving acyclovir cream and 4% of patients receiving placebo. The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each adverse reaction occurred in less than 1% of patients receiving acyclovir cream and placebo. Three patients on acyclovir cream and one patient on placebo discontinued treatment due to an adverse event.
An additional study, enrolling 22 healthy adults, was conducted to evaluate the dermal tolerance of acyclovir cream compared with vehicle using single occluded and semi-occluded patch testing methodology. Both acyclovir cream and placebo showed a high and cumulative irritation potential. Another study, enrolling 251 healthy adults, was conducted to evaluate the contact sensitization potential of acyclovir cream using repeat insult patch testing methodology. Of 202 evaluable subjects, possible cutaneous sensitization reactions were observed in the same 4 (2%) subjects with both acyclovir cream and placebo, and these reactions to both acyclovir cream and placebo were confirmed in 3 subjects upon re-challenge. The sensitizing ingredient(s) has not been identified.
The safety profile in patients 12 to 17 years of age was similar to that observed in adults.

Over Dose Effect

Overdosage by topical application of acyclovir cream is unlikely because of minimal systemic exposure.
There is no information available for overdose.

Pregnancy Comments

Risk summary
Acyclovir is minimally absorbed systemically following topical route of administration, and maternal use is not expected to result in fetal exposure to the acyclovir cream. Experience with topical acyclovir use in pregnant women over several decades, based on published literature including observational studies, has not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies with systemic exposure of acyclovir have been conducted.
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.

Pharmacokinetics

A clinical pharmacology study was performed with acyclovir cream in adult volunteers to evaluate the percutaneous absorption of acyclovir.
In this study, which included 6 male volunteers, the cream was applied to an area of 710 cm^2 on the backs of the volunteers 5 times daily at intervals of 2 hours for a total of 4 days. The weight of cream applied and urinary excretion of acyclovir were measured daily. Plasma concentration of acyclovir was assayed 1 hour after the final application. The average daily urinary excretion of acyclovir was approximately 0.04% of the daily applied dose. Plasma acyclovir concentrations were below the limit of detection (0.01 μM) in 5 subjects and barely detectable (0.014 μM) in 1 subject. Systemic absorption of acyclovir from acyclovir cream is minimal in adults.
The systemic absorption of acyclovir following topical application of cream has not been evaluated in patients <18 years of age.

Microbiology

Mechanism of Action:
Acyclovir is a synthetic purine deoxynucleoside analogue with cell culture and in vivo inhibitory activity against HSV types 1 (HSV-1) and 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.

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), vary greatly depending upon a number of factors. Using plaque-reduction assays on Vero cells, the EC50 values of acyclovir against herpes simplex virus isolates range from 0.09 to 59.9 µM (0.02 to 13.5 mcg/mL) for HSV-1 and from 0.04 to 44 µM (0.01 to 9.9 mcg/mL) for HSV-2.

Section 3: Composition / information on ingredients

Contains: Active: Each gram of acyclovir cream contains 50 mg (equivalent to 5% w/w) of acyclovir.

Material	Exposure Limit	CAS No.
Principle component:		
ACYCLOVIR	5mg/m^3	59277-89-3
Inactive Ingredients:		
CETOSTEARYL ALCOHOL	Not Found	67762-27-0
WHITE PETROLATUM	Not Found	8009-03-8
SODIUM LAURYL SULFATE	Not Found	151-21-3
MINERAL OIL	Not Found	8042-47-5
POLOXAMER 407	Not Found	9003-11-6
PROPYLENE GLYCOL	Not Found	57-55-6
PURIFIED WATER*	Not Found	7732-18-5

Section 4: First -aid measures

Inhalation Move to fresh air. If breathing is difficult, trained personnel should give oxygen. Call a physician if symptoms develop or persist. Under normal conditions of intended use, this material is not expected to be an inhalation hazard.

Skin Contact Immediately flush skin with plenty of water. Take off contaminated clothing and wash before reuse. Get medical attention if symptoms occur.

Eye contact Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

Ingestion If swallowed, rinse mouth with water (only if the person is conscious). If ingestion of a large amount does occur, call a poison control center immediately. Do not induce vomiting without advice from poison control center.

Most important symptoms / effects, acute and delayed None known.

Indication of immediate medical attention and special treatment needed No specific antidotes are recommended. Treat according to locally accepted protocols. For additional guidance, refer to the current prescribing information or to the local poison control information center.

General information In the case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves.

Section 5: Fire -fighting measures

Suitable extinguishing media Water. Foam. Dry chemical powder. Carbon dioxide (CO2).

Unsuitable extinguishing media None known.

Specific hazards arising from the chemical	During fire, gases hazardous to health may be formed.
Special protective equipment and precautions for firefighters	Self-contained breathing apparatus and full protective clothing must be worn in case of fire.
Fire fighting equipment/instructions	Move containers from fire area if you can do so without risk.
Specific methods	Use standard firefighting procedures and consider the hazards of other involved materials.
General fire hazards	This product will support combustion at elevated temperatures.

Section 6: Accidental Release Measures

Personal precautions, protective equipment and emergency procedures	Keep unnecessary personnel away.
Methods and materials for containment and cleaning up	Use water spray to reduce vapors or divert vapor cloud drift.
Environmental precautions	Large Spills: Stop the flow of material, if this is without risk. Dike the spilled material, where this is possible. Absorb in vermiculite, dry sand or earth and place into containers. Following product recovery, flush area with water. Small Spills: Wipe up with absorbent material (e.g. cloth, fleece). Clean surface thoroughly to remove residual contamination. Never return spills to original containers for re-use. For waste disposal. Avoid discharge into drains, water courses or onto the ground.
Environmental precautions	Avoid discharge into drains, water courses or onto the ground.

Section 7: Handling and Storage

Precautions for safe handling	Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Avoid prolonged exposure. Do not taste or swallow. When using, do not eat, drink or smoke. Wash hands thoroughly after handling.
Conditions for safe storage, including any incompatibilities	Keep away from heat, sparks and open flame. Store in original tightly closed container. Store away from incompatible materials.

Section 8: Exposure controls/personal protection

Biological limit values	No biological exposure limits noted for the ingredient(s).
Exposure guidelines	General ventilation normally adequate.
Appropriate engineering controls	
Eye/face protection	Not normally needed. If contact is likely, safety glasses with side shields are recommended.
Hand protection	Not normally needed. For prolonged or repeated skin contact use suitable protective gloves.
Other	Not normally needed. Wear suitable protective clothing as protection against splashing or contamination.
Respiratory protection	No personal respiratory protective equipment normally required. Use a NIOSH/MSHA approved respirator if there is a risk of exposure to dust/fume at levels exceeding the exposure limits.
Thermal hazards	Wear appropriate thermal protective clothing, when necessary.
General hygiene Considerations	Always observe good personal hygiene measures, such as washing after handling the material and before eating, drinking, and/or smoking. Routinely wash work clothing and protective equipment to remove contaminants. For advice on suitable monitoring methods, seek guidance from a qualified environment, health and safety professional.

Section 9: Physical and chemical properties

Physical State	Semi-solid.
Odor	Not available.
Color	White.

Section 10: Stability and reactivity

Reactivity	The product is stable and non-reactive under normal conditions of use, storage and transport.
Chemical stability	Material is stable under normal conditions.
Possibility of hazardous Reactions	Hazardous polymerization does not occur.
Conditions to avoid	Heat, flames and sparks. Contact with incompatible materials.
Incompatible materials	Alkaline metals.
Hazardous decomposition Products	None known. Irritating and/or toxic fumes and gases may be emitted upon the product's decomposition.

Section 11: Toxicological information

Information on likely routes of exposure

Inhalation Under normal conditions of intended use, this material is not expected to be an inhalation hazard.

Skin contact Health injuries are not known or expected under normal use.

Eye contact Health injuries are not known or expected under normal use. Direct contact with eyes may cause temporary irritation.

Ingestion Health injuries are not known or expected under normal use. May be harmful if swallowed. However, ingestion is not likely to be a primary route of occupational exposure.

Information on toxicological effects

Acute toxicity Expected to be a low hazard for usual industrial or commercial handling by trained personnel.

Components	Species	Test Results
ACYCLOVIR (CAS 59277-89-3)		
Acute		
Inhalation		
LC50	Rat	> 15.1 mg/l, 4 hours
Oral		
LD50	Rat	> 20 g/kg
CETOSTEARYL ALCOHOL (CAS 67762-27-0)		
Acute		
Oral		
LD50	Rat	> 5000 mg/kg
DODECYL SODIUM SULFATE (CAS 151-21-3)		
Acute		
Oral		
LD50	Rat	1288 mg/kg
PHARMACEUTICAL GRADE PETROLATUM (CAS 8009-03-8)		
Acute		
Oral		
LD50	Rat	> 15 g/kg
Chronic		
Oral		
NOAEL	Rat	>= 3000 mg/kg, 2 years

* Estimates for product may be based on additional component data not shown.

Skin corrosion/irritation Health injuries are not known or expected under normal use.

Irritation Corrosion - Skin
ACYCLOVIR
Acute dermal irritation. Tested at 5% in a cream: Irritation

Germ cell mutagenicity Health injuries are not known or expected under normal use.

Mutagenicity
ACYCLOVIR
Ames Assay
Result: Negative
C3H/T10 1/2 Cell Transformation Assay
Result: Negative
Chromosomal Aberration Assay In Vitro, Positive response only with levels much above equivalent of human therapeutic dose
Result: Positive
Species: Hamster
Chromosomal Aberration Assay In Vitro, human lymphocytes
Result: Equivocal
Cytogenetic Analysis In Vivo, bone marrow
Result: Negative
Species: Mouse
Mouse lymphoma cell (L5178Y TK) Assay
Result: Positive

Carcinogenicity	Carcinogenic effects are not expected as a result of occupational exposure. Contains a material (petrolatum) classified as a carcinogen by external agencies. These effects are suspected to be due to impurities that are not expected to be present in purified material used in this product.
ACYCLOVIR	2 year bioassay Result: Negative Species: Mouse 2 year bioassay Result: Negative Species: Rat
PHARMACEUTICAL GRADE PETROLATUM	>= 3000 mg/kg/day 2 year bioassay, oral administration Result: NOAEL Species: Rat Dermal application Result: Negative Species: Mouse

IARC Monographs. Overall Evaluation of Carcinogenicity

ACYCLOVIR (CAS 59277-89-3)	3 Not classifiable as to carcinogenicity to humans.

OSHA Specifically Regulated Substances (29 CFR 1910.1001-1050)

Not regulated.

Reproductive toxicity	This product is not expected to cause reproductive or developmental effects.
Fertility effects - Males and females	
ACYCLOVIR	0, Subcutaneous injection Result: NOAEL = 25 mg/kg/day; LOAEL = 50 mg/kg/day (decreased implantation efficiency, no effect on litter size) Species: Rat
Reproductivity	
ACYCLOVIR	Embryo-foetal development - Oral, sub-cutaneous administration Result: NOAEL = 50 mg/kg/day; no adverse foetal effects Species: Rabbit Embryo-foetal development - Oral, sub-cutaneous administration Result: NOAEL = 50 mg/kg/day; no adverse foetal effects Species: Rat
Specific target organ toxicity - single exposure	Not assigned.
Specific target organ toxicity - repeated exposure	Not assigned.
Aspiration hazard	Not established.
Further information	Caution - Pharmaceutical agent. Occupational exposure to the substance or mixture may cause adverse effects.

Section 12: Ecological information

Ecotoxicity: The product is not classified as environmentally hazardous. However, this does not exclude the possibility that large or frequent spills can have a harmful or damaging effect on the environment.

Section 13: Disposal consideration

Disposal instructions: Collect and reclaim or dispose in sealed containers at licensed waste disposal site. Do not discharge into drains, water courses or onto the ground. Dispose in accordance with all applicable regulations.

Section 14: Transport information

DOT
Not regulated as a dangerous good.
IATA
Not regulated as dangerous goods.
IMDG
Not regulated as dangerous goods.
Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code
Not established.

Section 15: Regulatory information

Generic Medicine. Acyclovir Cream, 5%; NDC no.: 72578-101-05 (5 gm)

Section 16: Other information

None

The information contained herein is based on the state of our knowledge. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product

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