### Denavir®

**brand of penciclovir cream, 1%**

**For Dermatologic Use Only Rx only**

Prescribing Information

**Descri**

Denavir (penciclovir) cream 1% contains penciclovir, an antiviral agent active against herpesviruses. Denavir is available for topical application as a 1% white cream. Each gram of Denavir contains 10 mg of penciclovir and the following inactive ingredients: cetomacrogol 1000 BP, cetylstearyl alcohol, mineral oil, propylene glycol, purified water and white petrolatum. Chemically, penciclovir is known as 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine. Its molecular formula is C10H15N5O3; its molecular weight is 232.3. It is a synthetic guanine derivative and has the following structure:  

![Chemical structure of penciclovir](image)

- Penciclovir is a white to pale yellow solid. At 20°C it has a solubility of 0.2 mg/mL in methanol, 1.3 mg/mL in propylene glycol, and 1.7 mg/mL in water. In aqueous buffer (pH 2) the solubility is 10.0 mg/mL. Penciclovir is not hygroscopic. Its partition coefficient in n-octanol/water at pH 2.5 is 0.024 (log Pow= -1.62).

CLINICAL PHARMACOLOGY

Microbiology

**Mechanism of Antiviral Activity:** The antiviral compound penciclovir has in vitro inhibitory activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2). It is not effective against herpesvirus hominis. Penciclovir is converted to penciclovir triphosphate (Penciclovir triphosphate) in vivo by viral thymidine kinase and cellular enzymes. Penciclovir triphosphate inhibits HSV-dependent DNA synthesis competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited.

**Antiviral Activity In Vitro** and **In Vivo:** In cell culture studies, penciclovir has antiviral activity against HSV-1 and HSV-2. Sensitivity test results, expressed as the concentration of the drug required to inhibit growth of the virus by 50% (IC50) or 95% (IC95) in cell culture, vary depending upon a number of factors, including the assay protocols. See Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Method of Assay</th>
<th>Virus Type</th>
<th>Cell Type</th>
<th>IC50 (mg/mL)</th>
<th>IC95 (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plaque Reduction</strong></td>
<td>HSV-1 (C6)</td>
<td>MRC-5</td>
<td>0.2-0.6</td>
<td>0.04-0.5</td>
</tr>
<tr>
<td></td>
<td>HSV-2 (C6)</td>
<td>MRC-5</td>
<td>0.8-2.1</td>
<td>0.1-0.8</td>
</tr>
<tr>
<td><strong>Virus Yield Reduction</strong></td>
<td>HSV-1 (C6)</td>
<td>MRC-5</td>
<td>0.40-0.5</td>
<td>0.40-0.5</td>
</tr>
<tr>
<td></td>
<td>HSV-2 (C6)</td>
<td>MRC-5</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>DNA Synthesis Inhibition</strong></td>
<td>HSV-1 (C6)</td>
<td>MRC-5</td>
<td>0.04</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>HSV-2 (C6)</td>
<td>MRC-5</td>
<td>0.04</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- (C6) = Clinical isolates. The latent state of any herpesvirus is not known to respond to any antiviral therapy.

Drug Resistance:

Penciclovir-resistant mutants of HSV can result from qualitative changes in viral thymidine kinase or DNA polymerase. The most commonly encountered acyclovir-resistant mutants that are deficient in viral thymidine kinase are also resistant to penciclovir.

### Pharmacokinetics

Measurable penciclovir concentrations were not detected in plasma or urine of healthy male volunteers (n=12) following single or repeat application of the 1% cream at a dose of 180 mg penciclovir daily (approximately 67 times the estimated usual clinical dose). From animal studies, penciclovir has a low potential for systemic absorption. The maximum penciclovir concentrations were measured in plasma and urine of healthy male volunteers (n=12) following single or repeat (twice daily) application of the 1% cream at a dose of 180 mg penciclovir daily. The maximum penciclovir concentration of all plasma and urine samples was below the limit of assay detection (0.1 mcg/mL and 10 mcg/mL, respectively).

However, for the purpose of inter-species dose comparisons presented in the following sections, an assumption of 100% absorption of penciclovir from the topically applied product has been used. Based on use of the maximally recommended topical dose of penciclovir of 0.05 mg/kg/day and an assumption of 100% absorption, the maximum theoretical plasma aUC0-24 hrs for penciclovir is approximately 0.129 mcg-hr/mL.

Carcinogenesis:

Two-year carcinogenicity studies were conducted with famciclovir (the oral prodrug of penciclovir) in rats and mice. An increase in the incidence of mammary adenocarcinoma (a common tumor in female rats of the strain used) was seen in female rats receiving 600 mg/kg/day (approximately 390x the maximum theoretical human exposure to penciclovir following application of the topical product, based on area under the plasma concentration-time curve) and 1000 mg/kg/day (approximately 750x the maximum theoretical human AUC for penciclovir). The incidence of mammary adenocarcinoma increased in female rats at 80 mg/kg/day and was dose-related in female rats at doses of 170 mg/kg/day and higher. A statistically significant increase in the incidence of mammary adenocarcinomas was also observed in female rats receiving 60 mg/kg/day (approximately 375x the maximum theoretical human AUC for penciclovir).

**Mutagenesis:** When tested in vitro, penciclovir did not cause an increase in gene mutation in the Ames assay using multiple strains of S. typhimurium or E. coli (at up to 20,000 mcg/plate), nor did it cause an increase in unscheduled DNA repair in human Methyl-Hex S3 cells (at up to 5,000 mcg/mL). However, an increase in chromosomal responses was seen with penciclovir in the L5178Y mouse lymphoma cell assay (at doses ≥1000 mcg/mL) and, in human lymphocytes incubated in vitro at doses ≥250 mcg/mL. When tested in vivo, penciclovir caused an increase in micronuclei in mouse bone marrow following the intravenous administration of penciclovir at doses ≥500 mcg/kg (1845x the maximum human dose, based on body surface area conversion). The systemic absorption of penciclovir following topical administration has not been evaluated in patients.

**Impairment of Fertility:** Testicular toxicity was observed in multiple animal species (rats and dogs) following repeated intravenous administration of penciclovir (160 mg/kg/day and 100 mg/kg/day, respectively, approximately 1155 and 325x the maximum theoretical human AUC). Testicular changes seen in both species included atrophy of the seminiferous tubules and reductions in epididymal sperm counts and/or an increased incidence of sperm with abnormal morphology or reduced motility. Adverse testicular effects were related to an increasing dose or duration of exposure to penciclovir.

**Teratogenic Effects:** Penciclovir did not cause teratogenic effects or adversely affect fertility or reproductive performance in female rats at doses of up to 100 mg/kg/day (36x the maximum human dose).

**Pregnancy:** There is no information on the effects of penciclovir on reproductive performance in pregnant women. Because animal reproduction studies are not always predictive of human response, penciclovir should be used during pregnancy only if clearly needed.

**Geriatric Use:** In 74 patients >65 years of age, the adverse events profile was comparable to that observed in younger patients.

**Adverse Reactions**

In two double-blind, placebo-controlled trials, 1516 patients were treated with Denavir (penciclovir cream) and 1541 with placebo. The most frequently reported adverse event was headache, which occurred in 5.3% of the patients treated with Denavir and 5.4% of the placebo-treated patients. The rates of reported local adverse reactions are shown in Table 2 below. One or more adverse reactions were reported by 2.7% of the patients treated with Denavir and 3.9% of placebo-treated patients. Two studies, enrolling 108 healthy subjects, were conducted to evaluate the dermatological safety of penciclovir cream at 5-fold higher concentration than those seen in the plasma. Therefore, a decision should be made whether to continue the drug, taking into account the importance of the drug to the mother. There are no data on the safety of penciclovir in newborns.

### Table 2—Local Adverse Reactions Reported in Phase III Trials

<table>
<thead>
<tr>
<th>Penciclovir n=1516 (%)</th>
<th>Placebo n=1541 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site reaction</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0.9</td>
</tr>
<tr>
<td>Local warmth</td>
<td>0.3</td>
</tr>
<tr>
<td>Rash</td>
<td>0.0</td>
</tr>
<tr>
<td>Pain</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash (erythematous)</td>
<td>0.1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Post-Marketing Experience**

The following events have been identified from worldwide post-marketing use of Denavir in treatment of recurrent herpes labialis cold sores in adults. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connections to Denavir cream.

**General:** Headache, oral/pharyngeal edema, paresthesia.

**Skin:** Application site reactions, aggravated condition, decreased therapeutic response, erythematous rash, local edema, pain, pruritus, urticaria, skin discoloration and urticaria.

**OVERDOSAGE:**

Since penciclovir is poorly absorbed following oral administration, adverse reactions related to penciclovir ingestion are unlikely. There is no information on overdosage.

**Dosage and Administration**

Denavir should be applied every 2 hours during waking hours for a period of 4 days. Treatment should be started as early as possible (i.e., during the prodrome or when lesions appear).

**How Supplied:**

Denavir is supplied in a 1.5 gram and 5 gram tube containing 10 mg penciclovir per gram. 1.5 gram NDC 50586-624-01; 5 gram NDC 44076-624-05 Store at controlled room temperature, 20°-25°C (68°-77°F) [see USP]

**QUESTIONS call 1-866-897-5002**

January 2013

Manufactured for Prestium Pharma, Inc.

Newtown, PA 18940

by Novartis Pharma GmbH, Wehr, Germany

Manufactured by Prestium Pharma, Inc. from Denca Asset, LLC.

©2013 Prestium Pharma, Inc.