PRODUCT MONOGRAPH

DENAVIR
(Penciclovir)

1% Topical Cream

Antiviral Agent

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PRODUCT MONOGRAPH

DENAVIR

(Penciclovir)

1% Topical Cream

THERAPEUTIC CLASSIFICATION

Antiviral agent

ACTIONS AND CLINICAL PHARMACOLOGY

Penciclovir is a substituted guanine analogue with selective activity against herpes simplex virus, which can cause recurrent herpes labialis. Penciclovir, an antiviral agent in the same class as acyclovir, is phosphorylated by viral thymidine kinase to the monophosphate, and then by cellular enzymes to penciclovir triphosphate in virus-infected cells. Penciclovir triphosphate inhibits viral DNA polymerase competitively with the natural substrate, deoxyguanosine triphosphate, and is incorporated into the extending DNA chain preventing chain elongation. Consequently, viral DNA synthesis and therefore viral DNA replication are inhibited. Inhibition of the virus reduces the period of viral shedding, limits the degree of spread and level of pathology, and thereby facilitates healing.

The phosphorylation of penciclovir in cells infected with herpes simplex virus is an important feature of its antiviral activity and selectivity. Penciclovir is inactive until phosphorylated, and it is only phosphorylated to high levels in virus-infected cells since viral thymidine kinase is essential for efficient phosphorylation. Antiviral selectivity is in part due to this preferential phosphorylation in infected cells, as well as to the greater affinity of penciclovir triphosphate for viral DNA polymerase as compared with cellular polymerases.

Percutaneous absorption of penciclovir across abraded and occluded dorsal skin of healthy male volunteers following topical application of penciclovir cream is minimal. Following the application of penciclovir cream at doses approximately 67-fold higher than the usual clinical dose (2.7 mg penciclovir/day based on application of 30 μL up to 9 times per day) penciclovir was not quantifiable in plasma or urine. The maximum daily systemic exposure to penciclovir following topical administration of the usual clinical dose can be estimated from this study to be substantially less than 0.51 mg/day.

Studies with intravenous penciclovir show that systemically available penciclovir undergoes minimal metabolism and is rapidly eliminated almost entirely by the kidneys (94%). Plasma half-life is approximately 2 hours. There is no evidence for accumulation on repeat (8 hourly) administration and pharmacokinetics appear linear over the dose range studies (2.5 to 20 mg/kg).

INDICATIONS AND CLINICAL USE

Denavir cream (penciclovir 1% topical cream) is indicated for the treatment of recurrent herpes labialis (cold sores) in adults.

CONTRAINDICATIONS

Denavir cream (penciclovir 1% topical cream) is contraindicated in patients with known hypersensitivity to the active ingredient or other constituents of the formulation, e.g. propylene glycol. Please refer to the Pharmaceutical Information Section for a listing of the inactive ingredients.

PRECAUTIONS

General:

Denavir cream (penciclovir 1% topical cream) should only be used for recurrent herpes labialis on the lips and face. It should not be applied inside the mouth, in or near the eyes or to the genital area. It is not recommended for application to mucous membranes.

There are no data at this time which show that the use of Denavir cream will prevent transmission of herpes simplex virus to another person.

The use of Denavir cream has not been clinically evaluated in immunocompromised patients. It is not recommended for use in immunocompromised patients.

No special precautions are required for the elderly, or hepatically impaired patient.

Although clinically significant viral resistance associated with the use of Denavir cream has not been observed, this possibility exists. (See VIROLOGY).

Pregnancy and Lactation:

The safety of penciclovir in human pregnancy has not been established. However, systemic adsorption of penciclovir following topical administration of penciclovir has been shown to be minimal. Denavir cream should only be used during pregnancy or in nursing mothers if the potential benefits are considered to outweigh the potential risks associated with treatment.

In animal studies, intravenous penciclovir doses a 1000 x greater than the recommended topical clinical dose of 2.7 mg/day did not show any embryotoxic or teratogenic effects. Neither were there any effects on male and female fertility and general reproductive performance.

Studies in rats show that penciclovir is excreted in the breast milk of lactating females given oral famciclovir (famciclovir; the oral form of penciclovir, is converted *in vivo* to penciclovir). There is no information on excretion of penciclovir in human milk.

Use in Children:

Safety and efficacy in children have not been established.

Geriatric Use:

In patients over 65 years of age (n = 74), the adverse events profile was comparable to that observed in younger patients.

Drug Interactions:

Clinical trial experience has not identified any interactions resulting from concomitant administration of topical or systemic drugs with Denavir cream.

ADVERSE EVENTS

Denavir cream (penciclovir 1% topical cream) has been well tolerated in human studies. Clinical trial experience has shown that in general there was no difference between Denavir™ cream and placebo in the rate or type of adverse reactions reported. The overall incidence of adverse events was slightly lower for the Denavir™ group (19.9%, 302 of 1516 patients) than for the placebo group (22.8%, 351 of 1541 patients).

The most frequent adverse reaction reported as related to treatment during clinical trials with Denavir cream was local irritation (burning, stinging and numbness) at the site of application. These adverse reactions occurred in less than 2% of patients in each group in the pivotal clinical trials.

The most frequent local adverse reactions reported during clinical trials with Denavir™ cream are shown in the following table.

Local Adverse Reactions (on Dose to within 30 Days) Reported in Phase III Trials

	Percent of Patients with Related* Adverse Events	
	Penciclovir N = 1516 %	**Placebo N = 1541 %**
Application site reaction	1.3	1.8
Hypesthesia/Local anesthesia	0.9	1.4
Taste Perversion	0.2	0.3
Pruritus	0.0	0.3
Pain	0.0	0.1
Rash (erythematous)	0.1	0.1
Allergic reaction	0.0	0.1

* Related Adverse Events include adverse events reported as related, probably related, possibly related and adverse events where the relationship was inaccessible or unknown.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose by topical application of Denavir cream (penciclovir 1% topical cream) is unlikely to occur due to minimal percutaneous absorption. A topical dose of approximately 67 times the human daily dose was shown to be well tolerated when applied topically to occluded and abraded skin for 4 days in a human volunteer study.

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 cream (penciclovir 1% topical cream) should be applied at approximately 2 hour intervals, during waking hours. Treatment should be continued for 4 days. Treatment should be started as early as possible after the first sign or symptom. Denavir cream has also been shown to be beneficial in accelerating lesion healing, reducing the duration of lesion pain and shortening the duration of viral shedding in patients who begin treatment later in the disease (i.e. when the papule or vesicle has developed).

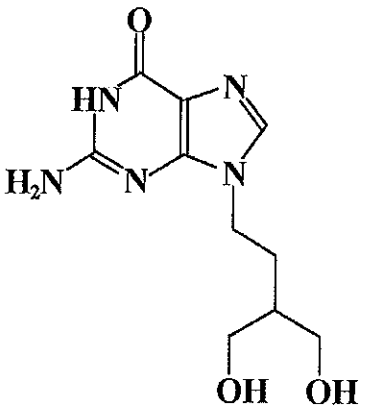
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: penciclovir

Chemical name: 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine

Molecular structure:



Molecular Formula: $C_{10}H_{15}N_5O_3$

Molecular Weight: 253.26

Description:

Penciclovir is a white to pale yellow solid with a melting point of 278°C with decomposition. At 20 °C, penciclovir is very slightly soluble in pH 6.97 aqueous buffer and slightly soluble in 1,2-propanediol (propylene glycol). The pKa of penciclovir is 3.2 and 9.8. The pH in saline is 5.1; pH in water is 5.6.

COMPOSITION

Denavir cream is a smooth, white cream containing 1% penciclovir.

Inactive ingredients consist of: white soft paraffin, liquid paraffin, cetostearyl alcohol, propylene glycol, purified water, cetomacrogol 1000.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15-30 °C). Do not freeze.

AVAILABILITY AND DOSAGE FORMS

Denavir cream (penciclovir 1% topical cream) is a smooth white cream supplied in 2g aluminum tubes.

VIROLOGY

Penciclovir has selective *in vitro* activity against herpes simplex virus (HSV, type 1 and type 2), varicella-zoster virus and Epstein-Barr virus. Limited activity against cytomegalovirus has also been shown.

In cells infected with herpes simplex virus, the viral thymidine kinase rapidly phosphorylates penciclovir to the monophosphate form. After further phosphorylation by cellular kinases, penciclovir triphosphate is produced, which inhibits herpes simplex virus DNA polymerase

competitively with deoxyguanosine triphosphate. Consequently, herpes simplex virus DNA synthesis and therefore viral replication, are selectively inhibited. In biochemical experiments, penciclovir triphosphate, behaves as a short DNA chain terminator. Limited elongation of the DNA chain can occur after incorporation. However, if concentrations of the reagents are modified to represent those present in cells infected with herpes simplex virus, penciclovir triphosphate is a more effective inhibitor of DNA chain elongation than acyclovir-triphosphate which is an obligate chain terminator. The clinical and biological significance of these results has not been established. Penciclovir triphosphate is stable within herpes simplex virus-infected cells and has a half-life of 10–20 hours. Phosphorylation of penciclovir in uninfected cells is very limited and furthermore, penciclovir triphosphate is only a weak inhibitor of cellular DNA polymerases. Cellular DNA synthesis in uninfected MRC-5 cells is not reduced after continuous treatment for 4 days at 100 μg/ml.

Antiviral susceptibility testing is used to provide information on the prevalence of resistant virus in the population, and also to determine the sensitivity of virus from an individual patient. As yet there is no internationally-approved methodology for herpes simplex virus susceptibility testing. The *in vitro* susceptibility of herpes simplex virus to penciclovir can be determined by a variety of different assays, and in common with other antivirals, both the choice of assay type and cell line influence the degree of antiviral activity. The plaque reduction assay is widely used to determine the antiviral susceptibility of herpes simplex virus, and results are expressed as the concentration of compound required to inhibit viral growth, as measured by plaque formation in cell monolayers, by 50% (IC_{50}; 50% inhibitory concentration). The IC_{50} values for penciclovir against herpes simplex virus isolates recovered to date from patients with herpes labialis range from 0.07–3.10 μg/ml in the plaque reduction assay in MRC-5 cells with a mean IC_{50} of 0.3 μg/ml.

Resistance

Herpes simplex viral thymidine kinase and viral DNA polymerase are the two viral enzymes involved in the selective antiviral action of both penciclovir and acyclovir. Accordingly, the

mechanism of viral resistance to these compounds is identical. The most common form of resistance to acyclovir (about 95% of acyclovir-resistant clinical isolates) is due to complete, or nearly complete, loss of viral thymidine kinase activity. Thymidine kinase-deficient mutants are almost invariably cross-resistant to penciclovir. Acyclovir-resistant mutants with an altered thymidine kinase or with an altered viral DNA polymerase are unusual. Acyclovir-resistant, thymidine kinase-altered mutants phosphorylate the natural nucleoside, thymidine, but are unable to phosphorylate acyclovir. Viral DNA polymerase from acyclovir-resistant DNA polymerase mutants is not inhibited by acyclovir triphosphate. Mutants from both of these classes may in some cases be cross-resistant to penciclovir depending on the specific mutation. Penciclovir-resistant thymidine kinase-deficient mutants are selected far more readily than other classes of mutant in cell culture, as is also the case for acyclovir.

Antiviral resistant mutations can occur naturally and are present in normal clinical isolates at a very low level. The background frequency of penciclovir-resistant herpes simplex virus determined in cell culture is very similar to that for acyclovir.

Pathogenicity

The pathogenicity of acyclovir-resistant herpes simplex virus mutants is generally reduced when assessed in animal models. Typically, thymidine kinase–deficient strains show the greatest attenuation, notably impaired replication, reduced virulence, and reduced ability to reactivate from latency. Because of the similarity in mechanism of action between acyclovir and penciclovir, the pathogenic characteristics of cross-resistant herpes simplex virus mutants selected with acyclovir are relevant to expected characteristics of resistant mutants selected with penciclovir.

In the clinic, reports of acyclovir-resistant herpes simplex virus in immunocompetent patients associated with clinical resistance to therapy are extremely rare. For severely immunocompromised patients, such as those with AIDS or bone marrow transplant recipients, the isolation of resistant virus is more common, and acyclovir-resistant herpes simplex virus is

more likely to be associated with clinical resistance to therapy than in immunocompetent patients. Important risk factors for the development of resistant herpes simplex virus are the degree of immunosuppression and the duration of antiviral therapy.

There has been one report describing possible transmission of an acyclovir-resistant herpes simplex virus mutant to a second individual. Given the similarities in viral resistance to acyclovir and penciclovir, this very low frequency of acyclovir-resistant herpes simplex virus transmission is likely to be predictive for penciclovir.

Surveillance data

Herpes simplex virus isolates have been collected from immunocompetent or immunocompromised patients participating in controlled, clinical trials with famciclovir (the oral form of penciclovir) or penciclovir (topical or intravenous). The frequency of penciclovir-resistant strains was 0.22% (4 resistant isolates among 1,843 isolates tested to date). There is no evidence of any change in the susceptibility to penciclovir of herpes simplex virus isolates from patients who have received either acute or suppressive antiviral therapy. Notably, among the four penciclovir-resistant isolates, two were obtained from patients on placebo and the remaining two were isolated from patients with recurrent herpes labialis on the first day of treatment with topical penciclovir, indicating that this was unlikely to be the result of selection. The disease course in these two patients treated with topical penciclovir was uneventful, and all subsequent isolates were sensitive to penciclovir.

The prevalence of penciclovir-resistant herpes simplex virus among immunocompetent patients in these clinical studies was 0.23% (3/1310 isolates), comparable to data on the prevalence of acyclovir-resistant herpes simplex virus (0.3–0.5%) in the immunocompetent population. Among herpes simplex virus isolates from patients with recurrent herpes labialis in the placebo-controlled trials of topical penciclovir, the prevalence of penciclovir-resistant virus was 0.20% (2/980 isolates).

PHARMACOLOGY

Clinical Trials:

In patients with recurrent herpes labialis, Denavir cream (penciclovir 1% topical cream) has been shown to significantly shorten the healing time of lesions and significantly reduce the duration of both lesion-associated pain and viral shedding.

Two pivotal, randomized, double-blind, placebo-controlled, patient-initiated trials were conducted. Patients were enrolled who had three or more recurrences of herpes labialis per year and more than 50% of these episodes were preceded by prodromal symptoms which resulted in classical lesions (vesicles / ulcers / crusts). Three thousand and fifty-seven patients (3057) received study medication : 1516 patients applied Denavir cream and 1541 patients applied the placebo formulation. A total of 2845 patients completed the trials; 1416 were penciclovir treated patients and 1429 were placebo recipients.

Healing

Denavir cream-treated patients lost classical lesions faster than placebo treated patients (95% CI ranged from 14 to 49%), with a reduction in median time to healing of approximately 1 day.

Pain

The time to loss of pain for Denavir cream-treated patients with classical lesions occurred significantly faster than for placebo recipients. Lesion pain was lost faster (95% CI ranged from 10 to 50%), with a reduction in median time of 0.5 to 1 day.

Viral Shedding

Denavir cream-treated patients ceased viral shedding faster (95% CI ranged from 10% to 80 %) compared with placebo recipients.

Fifty-four percent of patients (1645 / 3057) from the pivotal studies initiated medication early (during erythema or prodrome stages) compared with 44% (1335 patients) who initiated medication late (papule or vesicle stage). A subgroup analysis of early and late treatment effects revealed significant benefits for resolution of lesions, pain and viral shedding even when penciclovir was initiated at the papule or vesicle stage ($p<0.01$).

Pharmacodynamics:

There are no pharmacodynamic models for evaluating antiviral (HSV) activity in normal human subjects.

Animal - *in vivo*

Penciclovir produced few changes, and these were generally confined to the highest doses tested. Of note were the findings in the studies of cardiovascular, respiratory and renal function.

In the anaesthetized dog, penciclovir administered by intravenous bolus injection caused variable, slight effects on heart rate at low doses, and dose-related hypotension and prolonged increases in heart rate at 30 mg/kg and above; there were some ECG waveform disturbances at the higher doses. There was no indication of a selective effect on the autonomic nervous system. Penciclovir also caused increased heart rate in dogs receiving 50 mg/kg b.i.d. intravenously in 1- and 3- month repeat dose studies, but there were no adverse effects in monkeys receiving the same high dose for up to 1 month.

Renal function was significantly altered in rats following intravenous administration of penciclovir at the highest dose tested (160 mg/kg). In anaesthetized dogs (cardiovascular/respiratory study) crystalluria and reduced urinary osmolarity were detected at high intravenous doses (≥ 100 mg/kg). No effects on BUN, urinary electrolyte levels or creatinine clearance were however apparent. These findings may correlate with the nephrotoxicity observed in the intravenous repeat dose toxicology studies.

Pharmacokinetics:

Topical studies with Denavir™ cream (penciclovir 1% topical cream) and pharmacokinetic and biotransformation studies with penciclovir following intravenous administration have been carried out. It has not been possible to obtain pharmacokinetic and biotransformation data following application of penciclovir cream due to the low percutaneous absorption of penciclovir (less than 0.51 mg penciclovir/day).

Absorption:

Dermal Absorption:

Topical studies with Denavir cream (penciclovir (1% topical cream) in rat and man have shown that percutaneous absorption of penciclovir is low. In rats with abraded skin, approximately 7.0% of the administered penciclovir dose of 20 mg/kg (approx. 0.6 mg/cm^2 of skin) was absorbed, and absorption was even lower (0.2% of the dose) when the cream was applied to rats with unabraded skin.

Drug levels are achieved within the target skin layers as was shown in *in vitro* studies using intact cryo-preserved human skin and cryo-preserved human skin with tape-stripped stratum corneum. Radiolabelled penciclovir cream was applied to the surface of the explants and drug was detected in the epidermis and dermis of intact and tape stripped skin samples, although >99% of the dose remained on the skin surface. Only 0.02 and 0.31% of a radiolabelled dose

passed through intact and tape stripped skin respectively, thus absorption through human skin layers is inefficient in this *in vitro* model.

Tissue levels of penciclovir after application of excess cream to damaged skin in another *in vitro* model were 33 and 37 μg/g in dermis and epidermis, respectively, after 0.5 hours, and 217 and 319 μg/g tissue at 24 hours continuous exposure. These high levels are unlikely to be achieved *in vivo* in normal clinical usage.

Penciclovir concentrations were undetectable in the urine of healthy human subjects following application of 6 mL cream to abraded skin (approx. area 24 cm^2) three times a day for 4 days (approximately 67 times the estimated usual human daily dose).

These results support those obtained in the rat and confirm that penciclovir has a low potential for percutaneous absorption in man. Hence it is anticipated that very low systemic exposure to penciclovir will occur when Denavir cream is used therapeutically.

Distribution:

Following application of Denavir cream (penciclovir 1% topical cream) containing [^{14}C] penciclovir to intact human skin discs results showed negligible amounts of radioactivity permeated through the skin and into the receptor fluid (up to 0.31% of applied radioactivity over 24h). This is consistent with *in vivo* human studies which showed that the percutaneous absorption of penciclovir was minimal.

After intravenous administration, the volume of distribution of penciclovir in rat, dog and man is very similar at approximately 1 L/kg, indicating that penciclovir distributes beyond the plasma and probably slightly in excess of the total body water in these species.
The protein binding of penciclovir in the plasma of rat, dog and man over the concentration range of 2 - 20 μg/mL is low (range 6 - 24 %) and is comparable in the three species. In view of this, drug-drug interactions due to displacement from proteins are unlikely to occur with penciclovir.

Plasma protein binding of penciclovir is low (<20%) and penciclovir distributes freely between plasma and blood cells. Bioavailability is a less tangible concept with a topical presentation as serum levels may not be measurable or relevant.

Biotransformation:

No major metabolites of penciclovir have been detected in the urine of rat, dog or man following intravenous administration.

Excretion:

Radioactivity was rapidly excreted almost exclusively in the urine following intravenous administration of sodium [^{14}C] penciclovir to rat, dog, cynomolgus monkey and healthy human subjects. Intravenous studies with sodium penciclovir in rat, dog, and man have shown that, in all three species, penciclovir is cleared almost exclusively by the kidney. In rat and man, evidence has been obtained that net tubular secretion occurs, since renal clearance is greater than the glomerular filtration rate. Elimination of penciclovir is rapid in all species, terminal half-lives being less than 1 h in the rat and approximately 2 h in dog and man. In both rat and dog, AUC values for penciclovir increase with dose following repeated intravenous administration of the sodium salt and generally the increase is approximately dose proportional.

In human studies most of the administered radioactivity was excreted in 24 hours of dosing (approximately 91%). Mean total recoveries of administered radioactivity in urine and feces was 97% indicating that very little retention of radioactive material occurred.

A small but clinically insignificant reduction in mean renal clearance of penciclovir is observed in females compared with males, and in the elderly compared to the young. In both cases the differences observed are thought to relate to gender- and age-related decreases in renal function, respectively.

Furthermore, mean elimination half-life estimates for females (2.0 h) and the elderly (2.7 h) do not necessitate a dosage adjustment according to age or gender in those patients with normal or mildly impaired renal function (See Dosage and Administration).

Elderly:

The pharmacokinetics of penciclovir in healthy, elderly (65 - 81 years) and healthy, young (19 - 36 years) male subjects (n=18) was investigated following a single intravenous infusion (1 h) of 5 mg/kg penciclovir.

Plasma clearance of penciclovir was reduced (on average by 42%) in elderly compared to healthy, young individuals. Hence, exposure to penciclovir as measured by Cmax and AUC (0-inf) and 42% for Cmax, values were still within limits shown to be well tolerated by healthy, young individuals. Furthermore, whilst the elimination half-life is longer in elderly [mean (sd) 2.63 (0.38)h] compared to young [mean (sd) of 2.02 (0.42)h], the extent of the change (at maximum 0.83 h) is of no clinical significance.

Renal impaired patients:

The pharmacokinetics of penciclovir following a single intravenous infusion (1 h) at 5 mg/kg, was determined in male (n=12) and female (n=10) subjects with varying degrees of renal function. Penciclovir plasma clearance estimates in subjects classified as having mild, moderate or severe renal impairment were reduced on average by 18%, 46% and 82%, respectively, compared to values in healthy subjects with normal renal function.

The mean estimate of AUC in subjects with normal renal function was 83%, 51% and 15% of values reported in subjects with mild, moderate and severe renal impairment, respectively. For Cmax, mean estimates in subjects with normal renal function were 101%, 86% and 70 % of values reported in mild, moderate and severely impaired patients, respectively.

However, as previously noted these results are of little significance given the minimal exposure to penciclovir following topical administration.

TOXICOLOGY

Penciclovir has undergone a comprehensive toxicological evaluation; principal findings from the key studies are summarized below.

Acute Toxicity Studies

Penciclovir has a low order of acute toxicity, with intravenous median lethal doses of between 700 and 1000 mg/kg in rats and 1200 mg/kg in mice. The majority of adverse effects were indicative of central nervous system disturbances, undoubtedly reflecting the high doses used in the studies to assess general pharmacological actions.

Subacute Toxicity Studies

In rats and rabbits penciclovir cream was applied once daily for 28 consecutive days at a dosage of 2 g/kg body weight, resulting in a nominal dose of 100 mg penciclovir/kg/day. There were no signs of irritancy in the rats and only occasional slight erythema in rabbits at the shaved, abraded and occluded sites of application

Slight reductions in red blood cell parameters were seen in rats in both the 28-day and 13-week intravenous studies. However, there was no evidence of an effect on the bone marrow and the finding is considered to be a result of intravascular haemolysis given the lack of *in vitro* haemolysis in a buffered system. Also, the effect was confined to the highest doses administered, 160 mg/kg/day in the 28-day study and 80 mg/kg/day in the 13-week study, and there was a return to normal on withdrawal of treatment.

Carcinogenicity

The carcinogenic potential of penciclovir has been evaluated in 2-year rat and mouse studies in which famciclovir was administered in the diet. Although an increase in the number of high dose female rats with malignant mammary tumours was apparent, the pattern of the response did not suggest that a genotoxic mechanism was implicated in the development of these tumours. Furthermore, there was a clear no-effect dose. This, together with the extremely low dosage of topical penciclovir and short duration of treatment, leads to the conclusion that the observation in the rat carcinogenicity study dose not indicate a carcinogenic risk to patients using Denavir™ cream (penciclovir 1% topical cream).

The photocarcinogenic potential of Denavir™ (penciclovir 1% topical cream) has not been evaluated. There is, however, no evidence to suggest that penciclovir drug substance might interact with sunlight, as the compound shows no significant absorption or degradation in the relevant portions of the UV spectrum (UV-A or UV-B).

Mutagenicity Studies

The results of a wide range of mutagenicity studies *in vitro* and *in vivo* indicate that penciclovir does not pose a genetic risk to man. Penciclovir, in common with other drugs of this class, has been shown to cause chromosomal damage *in vitro*, but did not induce sister chromatid exchange in mammalian cells or gene mutation in bacterial or mammalian cell systems. Inhibition of mitosis and prolonged cell cycle were seen in a mammalian cell system, but there was no evidence of increased DNA repair *in vitro*.

Penciclovir was negative in *in vivo* tests for repairable DNA damage, but in common with other nucleoside analogues such as acyclovir, caused significant chromosomal damage *in vivo* (positive in mouse micronucleus assay) . However, the effects *in vivo* occurred only following very high intravenous doses (500 mg/kg and above) with an apparent threshold at about 300 mg/kg, below which no increases in micronuclei were seen.

In view of the potential for high local concentrations in the skin at the site of application of Denavir (penciclovir 1% topical cream) (see Dermal Absorption, above), and the observation of mitotic inhibition in some *in vitro* assays, the potential for effects on epithelial regeneration cannot be ruled out. However, no such detrimental effects on healing have been observed in clinical trials.

Reproduction

Intravenously administered penciclovir was without adverse effect on reproductive function, despite evidence of maternal and paternal toxicity at the highest doses used (80 mg/kg/day in the rat, 60 mg/kg/day in the rabbit). There were no effects on the fertility or general reproductive performance (Segment I) of male or female rats, nor were there adverse findings in the undosed F1 generation of the penciclovir-treated mothers.

In rats and rabbits there were no adverse effects on the course and outcome of pregnancy (Segment II), and penciclovir also had no effect on post-natal growth, survival and development of offspring from treated female rats.

It is known that penciclovir is excreted in the milk of lactating female rats given oral famciclovir, but the proportion of the administered dose received by each pup was extremely low (approx. 0.2%).

Degenerative changes of the testicular epithelium were noted in some animal studies with intravenous penciclovir, although these were confined to the highest dose groups. This is a common finding with drugs of this class.

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