SUMMARY OF PRODUCT CHARACTERISTICS

Summary of product characteristics

1. Name of the medicinal product

Acyclovir Denk 5% Cream

2. Qualitative and quantitative composition

2.1 General description

White, smooth creamous mass.

2.2 Qualitative and quantitative composition

Active ingredient: aciclovir.
1 g cream contains 50 mg aciclovir.

Excipients: cetyl alcohol, propylene glycol
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Cream.

4. Clinical particulars

4.1 Therapeutic indications

For the palliative treatment of pain and pruritus in recurrent genital and labial herpes.

Note:
In order to achieve the best results, the cream should be applied as soon as the first signs of herpes infection become noticeable (burning, itching, tension, reddening). Once the skin efflorescence crusts over, virustatic treatment with acyclovir cream is no longer useful.

4.2 Posology and method of administration

Posology
Acyclovir Denk 5 % Cream should be applied five times daily at approximately 4 hourly intervals thinly to the affected areas.

Mode of application
Acyclovir Denk 5 % Cream should be applied with a wadding stick, by applying the amount of cream required to cover the infected parts of the skin. When applying, it should be insured, that not only the visible signs of herpes (blisters, swelling, reddening) are covered by the cream, but that the surrounding areas of the skin are also treated. If applied by hand, the hands should be cleaned thoroughly before and immediately after application, in order to ensure that there is not additional infection (e.g. through bacteria) of the damaged area of the skin and that there is no transmission of the virus to non infected mucous membrane and other skin areas.

Duration of treatment
The duration of treatment is generally 5 days.
In individual cases the treatment should be continued, until the blisters become crusty or heal.
The duration of treatment should however not exceed 10 days.

4.3 Contraindications

Hypersensitivity to the active substance aciclovir, to valaciclovir or to any of the excipients.

4.4 Special warnings and precautions for use

In patients with severe disorders of the endogenous immune system, systemic administration of aciclovir is the treatment of choice, as the possibility of dissemination, particularly among these patients, cannot be excluded.

Acyclovir Denk 5% Cream must not be applied to mucous membranes (e.g. in the oral cavity, on the eye or in the vagina), as signs of local irritation can otherwise be expected.

When treating with Acyclovir Denk 5% Cream in the genital or anal region, the tear resistance of concomitantly used condoms may be reduced, thus impairing the safety of condoms, due to the white vaseline and liquid paraffin (excipients) used as ingredients in the cream.

Propylene glycol may cause skin irritation. Cetyl alcohol may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

Not known.

4.6 Pregnancy and lactation

Pregnancy

The available data on use during pregnancy have shown no increased malformation rate compared to the normal population. As the malformations that occurred were not homogeneous, no same cause can be imputed.

This medicinal product should only be used during pregnancy after careful consideration of the benefit-to-risk ratio.

Lactation
Following systemic use, aciclovir is excreted in human milk. However, the dose that a child would absorb via breast-feeding is negligible following maternal use of Acyclovir Denk 5% Cream.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse drug reactions are classified as follows:

very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000)
not known (cannot be assessed on the basis of the available data).

Skin and subcutaneous tissue disorders
Uncommon: Transient burning or stinging following application of Acyclovir Denk 5 % Cream; drying and flaking of the treated skin; itching.

Rare: Erythema, contact dermatitis developed after administration of Acyclovir Denk 5 % Cream. Allergology test which were performed, showed that in most cases the excipients in the cream and not the active ingredient itself were the cause. Contact dermatitis can be identified, in that the above mentioned side effects are more pronounced and that they spread to parts of the skin which was not treated with the cream.

Immune system disorders
Very rare: immediate-type hypersensitivity reactions including angioedema.

4.9 Overdose

No unfavourable effects are expected as a result of accidental oral ingestion of up to 10 g cream containing 500 mg aciclovir.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Guanosine analogue, antiviral agent
DNA polymerase preventing agent
ATC Code: D06B B03

Acyclovir is a pharmacologically inactive substance, which becomes virustatic only after penetrating a cell, which is infected with herpes simplex or varicella zoster viruses.

This activation of acyclovir is catalysed through herpes simplex or varicella zoster viruses thymidine-kinase, an enzyme, which the virus urgently requires for replication.

The following individual steps take place:

1. Aciclovir penetrates the herpes infected cells after application in increased number.
2. The virus thymidine kinase, present in these cells, phosphorylizes aciclovir to aciclovir monophosphate.
3. Cellular enzymes change the aciclovir monophosphate into the actual antiviral agent aciclovir triphosphate.

4. Aciclovir triphosphate has a 10 to 30 times stronger affinity to the virus-DNA-polymerase than to cellular-DNA-polymerase and in this way selectively inhibits the activity of the viral enzyme.
5. In addition, the virus-DNA-polymerase, builds aciclovir into the virus DNA, which results in a chain breakdown of DNA synthesis.

These individual steps result, in total, in a very effective reduction of virus production.

Plaque reduction tests demonstrated that, in order to impede growth of HSV infected viral cells an average of 0.1 µmol aciclovir/l is required (cell culture from the kidney parenchyma of the green african monkey), in non infected cells on the other hand 300 µmol aciclovir/l is required. One can therefore determine for cell cultures therapeutic indices up to 3000.

Range of activitiy in vitro:

Very sensitive:	Herpes simplex virus type I and II Varicella zoster virus
Sensitive:	Epstein Barr virus
Slightly sensitive to resistant:	Zytomegalie virus
Resistant:	RNS virus Adenovirus Smallpox virus

5.2 Pharmacokinetic properties

Examining the resorption of aciclovir from the cream:
The cream was applied to 6 probands five times per day, over four successive days. The cream was applied to the skin of the back and was spread over an area of 710 cm^2 until no more cream was visible.

During the tests aciclovir could not be detected in the serum. The limit of detection of aciclovir was less than 0.01 µmol/l. On the second day a detectable concentration of aciclovir was found in the urine, whereby the concentrations grew slightly during treatment and reached a level of 0.6 µmol/l on the fourth day. This value corresponds to less than 0.1 % of the amount of aciclovir applied to the skin.
Although these values show that there is a minimal resorption of aciclovir from the cream, the actual extent of concentrations demonstrates that no systemic action is to be expected.

No measurable aciclovir concentrations could be determined in the blood after use of the cream.

5.3 Preclinical safety data

Investigation of local tolerability of the cream:
The cream was applied to rabbits, on damaged and undamaged skin, over a period of 21 days at several intervals per day. Repeated application did result in some very limited irritation.

No further studies have been reported since the amount of active ingredient resorbed from the cream could not be detected in the plasma. (Please refer to 5.2 Pharmacokinetic properties).

6. Pharmaceutical particulars

6.1 List of excipients

stearoyl macrogolglycerides, dimeticone 350, cetyl alcohol, white soft paraffin (vaseline), liquid paraffin, propylene glycol, purified water.

6.2 Incompatibilities

No incompatibilities have been reported to date. However, Acyclovir Denk 5% Cream should not be diluted or used as a base for the absorption of other medicinal substances.

6.3 Shelf life

The shelf life of Acyclovir Denk 5 % Cream is 3 years.

6.4 Special precautions for storage

Store below 25 ºC. Do not refrigerate or freeze.
Do not use after the expiry date which is stated on the carton.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

Tubes of 7 g cream.
The tubes consist of aluminium coated with a protective lacquer.

6.6 Special precautions for disposal

No special requirements.

7. Marketing authorisation holder

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. Marketing authorisation number in Germany

24819.00.00

9. Date of first authorisation in Germany

12.12.1995

10. Date of revision of the text

December 2013

11. Prescription status

Over the counter medicine