SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acyclovir Denk 200

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: aciclovir

Each tablet contains 200 mg aciclovir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Round, white, biconvex tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acyclovir Denk 200 is indicated for the treatment of herpes simplex virus (HSV) infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).

An attempt at preventive treatment is indicated in adult patients suffering from very severe forms of very frequently recurring genital herpes simplex infections.

4.2 Posology and method of administration

Posology

Adults

For herpes simplex infections
One single dose of 200 mg aciclovir 5 times throughout the day at intervals of 4 hours.

For prophylaxis against severe forms and very frequently recurring genital herpes simplex infections
Immunologically healthy patients are given a single dose of 200 mg aciclovir 4 times daily at intervals of 6 hours. Alternatively, 400 mg aciclovir can also be administered daily at intervals of 12 hours. In individual cases, effective prophylaxis can also be achieved with a dosage of 200 mg aciclovir 3 times daily at intervals of 8 hours or 200 mg aciclovir twice daily at intervals of 12 hours.

If recurrence (breakthrough infection) occurs despite this daily total dose of 800 mg, 200 mg aciclovir should be administered 5 times throughout the day at intervals of 4 hours for 5 days, as stated in the dosage for herpes simplex infections. Thereafter, the above dosage is given again.

For prophylaxis, immunosuppressed patients are given a single dose of 200 mg aciclovir 4 times daily at intervals of 6 hours.

Severely immunosuppressed patients, e.g. after organ transplants, can be administered a single dose of 400 mg aciclovir 4 times daily at intervals of 6 hours. Alternatively, aciclovir powder for intravenous infusion can also be administered, especially in patients with impaired enteral absorption.

Note
Possible development of resistance has been described in patients with immunosuppression. This should be considered during administration.

Paediatric population
For the treatment of herpes simplex infections, the adult dose is given to children over 2 years and half the adult dose to children below 2 years.

Renal impairment (see section 5)

Indication	Creatinine clearance (ml/min/1.73 m^2)	Serum creatinine (µmol/l) or (mg/dl)		Single-dose posology
		Women	Men	
Herpes simplex infections	< 10	> 550 > 6.22	> 750 > 8.48	200 mg aciclovir twice daily every 12 hours

Method of administration
The tablets should preferably be taken after meals with some liquid.

Especially in patients with impaired renal function (see section 5), adequate fluid intake should be ensured during treatment.

Duration of treatment
For herpes simplex infections, the duration of treatment is 5 days. However, this can be extended depending on the patient's clinical status.

For the prevention of herpes simplex infections in immunologically healthy patients, the duration of treatment is dependent on the severity of disease and frequency of recurrence. However, it should not exceed a period of 6–12 months.

For prophylaxis against herpes simplex infections in severely immunosuppressed patients, the duration of administration is determined by the severity of immunosuppression and the duration of the risk of infection.

4.3 Contraindications

Hypersensitivity to aciclovir, valaciclovir or to any of the excipients listed in section 6.1

As there are still no available data on the prophylactic use of aciclovir 200 mg tablets in patients with impaired renal function or anuria, the product should not be used under these conditions.

4.4 Special warnings and precautions for use

Patients with impaired renal function and elderly patients
Aciclovir is renally eliminated; the dose must therefore be reduced in patients with impaired renal function (see section 4.2). In elderly patients, as reduced renal function is probable, the need for dose

reduction should be considered for this patient group. Both elderly patients and patients with impaired renal function are at greater risk of developing neurological side effects and should therefore be carefully observed for the occurrence of such effects. Based on the cases reported, these reactions were generally reversible upon discontinuation of treatment (see section 4.8).

In patients with a severely impaired immune system, prolonged or repeated administration of aciclovir can lead to selection of viral strains with reduced sensitivity that do not respond to continued treatment with aciclovir.

Hydration status
In patients taking high aciclovir doses, adequate fluid intake should be ensured.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been found to date.

Aciclovir is mainly excreted through the kidneys in unchanged form via active tubular secretion in the urine. Co-medications that are also excreted via this mechanism can increase the plasma concentration of aciclovir. Probenecid and cimetidine increase the AUC of aciclovir via this mechanism and hence lead to reduced renal excretion of aciclovir. Similar increases in the plasma AUC of aciclovir and the inactive metabolite of mycophenolate mofetil, an immunosuppressant used in transplant patients, have been observed when these medicinal products were co-administered.
However, due to the wide therapeutic range of aciclovir, no dose adjustment is required.

4.6 Pregnancy and lactation

Pregnancy
Data from a limited number of exposed pregnancies do not indicate any adverse effects for aciclovir on the course of pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data is available. Animal studies do not indicate direct or indirect harmful effects in relation to pregnancy, embryonal/foetal development, parturition or postnatal development.
Caution must be exercised when used during pregnancy

Lactation
Aciclovir is excreted in breast milk. If the mother requires systemic treatment as a result of a severe infection, breast-feeding should be discontinued owing to the risk of infection. Otherwise, treatment should be local, in order to enable breast-feeding to be continued.

4.7 Effects on ability to drive and use machines

In view of the effects on the ability to drive and use machines, the patient's state of health and the adverse effect profile of aciclovir should be taken into consideration.
The effect of aciclovir on the ability to drive or use machines has not been investigated. No adverse effects on these activities can be derived solely on the basis of the pharmacology of the active substance alone.

4.8 Undesirable effects

The following frequencies are used for the evaluation of undesirable effects:

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 estimated from the available data)

Blood and lymphatic system disorders
Very rare: anaemia, leukopenia, thrombocytopenia

Immune system disorders
Rare: anaphylactic reactions

Psychiatric disorders and nervous system disorders
Common: dizziness, headache
Very rare: general physical restlessness, confusional states, tremor, ataxia, dysarthria, hallucinations, symptoms of psychoses, seizures, drowsiness, encephalopathy, coma

The above-mentioned events were generally reversible and were mainly reported in patients with impaired renal function with or without predisposing factors (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Rare: dyspnoea

Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea, abdominal pain

Hepatobiliary disorders
Rare: transient elevations of bilirubin and liver enzymes
Very rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: pruritus, skin rash (including photosensitivity reactions)
Uncommon: urticaria, diffuse alopecia
As this type of hair loss is ascribed to a large number of pathologies and medicinal products, the relationship with the use of oral medications containing aciclovir is unclear.
Rare: angioedema.

Renal and urinary disorders
Rare: elevation of serum urea and creatinine
Very rare: acute renal failure, nephralgia
Nephralgia may be associated with renal failure.

General disorders and administration site conditions
Uncommon: fatigue, fever

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms
Aciclovir is only partially absorbed from the gastrointestinal tract.
After ingestion of single doses up to 20 g aciclovir, no toxic effects have generally occurred. An accidental, repeated overdose of orally administered aciclovir over several days was associated with gastrointestinal symptoms (nausea and vomiting) and neurological symptoms (headache and confusion).

An overdose of intravenously administered aciclovir led to an increase in serum creatinine and blood urea nitrogen and subsequently to renal failure.
Neurological effects including confusion, hallucination, agitation, seizures and coma have been described in association with this intravenous overdose.

Procedures
Patients should be observed for signs of toxicity. The elimination of aciclovir from the blood can be significantly accelerated by haemodialysis. Thus, haemodialysis can be considered in the event of a symptomatic overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: guanosine analogue, antiviral, viral DNA polymerase inhibitor
ATC code: J05AB01

Aciclovir is a pharmacologically inactive substance which does not become an antiviral agent until after penetration into a cell infected with herpes simplex viruses (HSV) or varicella zoster viruses (VZV). This activation of aciclovir is catalysed by HSV- or VZV thymidine kinase, an enzyme that viruses particularly need for their replication.
In simple terms, one can say that the virus synthesises its own antiviral agent. In more detail, the following steps occur:

1. Aciclovir preferentially penetrates herpes-infected cells.
2. The viral thymidine kinase present in these cells phosphorylates aciclovir to aciclovir monophosphate.
3. Cellular enzymes convert aciclovir monophosphate to aciclovir triphosphate, the actual antiviral agent.
4. Aciclovir triphosphate has a 10-30 times greater affinity to viral DNA polymerase than cellular DNA polymerase and hence selectively inhibits activity of the viral enzyme.
5. Furthermore, the viral DNA polymerase incorporates aciclovir into the viral DNA, resulting in a chain termination during DNA synthesis.

Overall, these individual steps lead to a highly effective reduction in viral production.

In the plaque reduction test, an ED_{50} inhibition value of 0.1 µmol aciclovir/l was measured for HSV-infected vero cells (= cell cultures from the renal parenchyma of the green African monkey), whereas an ED_{50} value of 300 µmol aciclovir/l was required to prevent the growth of non-infected vero cell cultures.
Hence, an inhibitory concentration ratio of up to 3000 is determined for cell cultures.

Spectrum of activity *in vitro*
Very sensitive: herpes simplex virus types I and II, varicella zoster virus
Sensitive: Epstein-Barr virus
Partially sensitive to resistant: cytomegalovirus
Resistant: RNA viruses, adenoviruses, pox viruses

5.2 Pharmacokinetic properties

Absorption
Aciclovir is only partially absorbed from the gastrointestinal tract. After repeated oral administration of 200 mg, 400 mg and 800 mg aciclovir at an interval of 4 hours 5 times a day, mean peak plasma levels determined at steady state are 3.02 ± 0.5 µmol/l (200 mg), 5.21 ± 1.32 µmol/l (400 mg) and

8.16 ± 1.98 µmol/l (800 mg), respectively. These values are reached after about 1.5 ± 0.6 hours. The corresponding plasma baseline values are respectively 1.61 ± 0.3 µmol/l (200 mg), 2.59 ± 0.53 µmol/l (400 mg) and 4.0 ± 0.72 µmol/l (800 mg) about 4 hours after oral administration of aciclovir. 24 hours after discontinuation of aciclovir tablets, aciclovir is no longer detectable in the body.

Paediatric population
In immunosuppressed children aged 3–11 years who were orally administered aciclovir at doses of 400 mg, equivalent to 300-650 mg aciclovir/m^2 BSA, 5 times daily, mean peak plasma levels of 5.7–15.1 µmol/l were determined. In infants aged 1-6 weeks after oral administration of 600 mg aciclovir/m^2 BSA every 6 hours, peak plasma levels of 17.3 and 8.6 µmol/l were respectively measured.

In neonates (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C^{ss}max was found to be 61.2 µmol/l (13.8 µg/ml) and the C^{ss}min to be 10.1 µmol/l (2.3 µg/ml). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 µmol/l (18.8 µg/ml) and Cmin of 14.1 µmol/l (3.2 µg/ml).

Based on the biexponential progression of aciclovir kinetics, it can be concluded that aciclovir reaches tissue and the organs at high concentrations, from whence elimination is slow.

The steady-state volume of distribution is 50 ± 8.7 l/1.73 m^2 in adults and 28.8 ± 9.3 l/1.73 m^2 in neonates and infants up to 3 months.
Values between 9 and 33% have been determined for protein binding.

Distribution
Animal trials confirm that, compared to the serum level, higher aciclovir levels are reached in the intestines, kidney, liver and lung, whilst lower levels are reached in the muscle, heart, brain, ovaries and testes of the animals.

Post-mortem investigations in humans have revealed that aciclovir accumulates in saliva, vaginal secretions, in the vesicular fluid of herpes blisters and some organs. 50% of the corresponding serum concentrations are reached in the cerebrospinal fluid.

Biotransformation and elimination
In patients with healthy kidneys, aciclovir is renally eliminated in unchanged form (62–91%) and as 9-carboxymethoxy methyl guanine (10–15%). After IV administration of aciclovir, plasma half-lives ($t_{1/2ß}$) of 2.87 ± 0.76 hours were determined for adults and 4.1 ± 1.2 hours for neonates and infants up to 3 months. Aciclovir undergoes both glomerular filtration and tubular secretion. If aciclovir is given one hour after administration of 1 g probenecid, the plasma half-life ($t_{1/2ß}$) is prolonged by 18% and the area under the plasma concentration-time curve is increased by 40%. With a bioavailability of about 20%, approximately 80% of the total aciclovir dose is excreted with the faeces.

Renal impairment
In patients with chronic renal insufficiency, the mean plasma half-life is about 19.5 hours. The mean plasma half-life during haemodialysis is 5.7 hours. During haemodialysis, aciclovir plasma levels fall by about 60%. In patients with impaired renal function, there is a risk of accumulation at creatinine clearance values of 10 ml/min/1.73 m^2 at a dosage of 5 x 200 mg/day. Hence, a dose reduction at this value or below is indicated (see also section 4.2).

5.3 Preclinical safety data

There are no insights from chronic toxicity studies leading to the suspicion that previously unknown side effects could occur in humans. What is more, *in vivo* and *in vitro* studies revealed no evidence of a reproduction-toxic, mutagenic or carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Povidone K25
Sodium starch glycolate
Magnesium stearate
Maize starch
Colloidal anhydrous silica.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters

Pack size: 25 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER IN GERMANY

31346.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

29/05/1995

10. DATE OF REVISION OF THE TEXT

01/2019

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription