SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acyclovir Denk 200

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Aciclovir
Each tablet contains:
Aciclovir……200 mg

Excipient with known effect: Each tablet contains less than 1 mmol sodium (23 mg).

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, in particular genital herpes infections of the skin and mucosa (initial and frequently recurring genital herpes), excluding herpes simplex infections in neonates and severe HSV infections in immunocompromised children.
- for prophylactic treatment in adult patients with very severe and very frequently recurring forms of genital herpes simplex infections.

4.2 Posology and method of administration Posology

Adults

Herpes simplex infections
A single dose of 200 mg aciclovir (1 tablet) five times daily at intervals of 4 hours.

Prophylaxis of severe and very frequently recurring forms of genital herpes simplex infection
Immunocompetent patients
Immunocompetent patients receive a single dose of 200 mg aciclovir (1

tablet) four times daily at intervals of 6 hours.

Alternatively, it is also possible to take 400 mg aciclovir (2 tablets) twice daily at intervals of 12 hours. In individual cases, effective prophylaxis can also be achieved with a dose of 200 mg aciclovir (1 tablet) three times daily at intervals of 8 hours, or 200 mg aciclovir (1 tablet) twice daily at intervals of 12 hours.

If recurrence occurs despite prophylactic treatment (break-through infection), dosing should take place as for herpes simplex infections, namely 200 mg aciclovir (1 tablet) five times daily at intervals of 4 hours, for 5 days. After this, the above-mentioned dosage should be given once again.

Immunocompromised patients
For prophylactic treatment, immunocompromised patients receive a single dose of 200 mg aciclovir (1 tablet) four times daily at intervals of 6 hours.

Severely immunocompromised patients
Severely immunocompromised patients, e.g., after organ transplantation, can be given a single dose of 400 mg aciclovir (2 tablets) four times daily at intervals of 6 hours.

Paediatric population

Herpes simplex infections
For the treatment of herpes simplex infections, children over 2 years receive the adult dosage, and children under 2 years receive half the adult dosage.

Dosage in elderly patients
In elderly patients, the possibility of renal impairment must be considered, and the dosage should be adjusted accordingly (see section “Dosage in renal impairment” below).

Adequate fluid intake should be maintained at all times in elderly patients taking high doses of aciclovir.

Dosage in renal impairment
Caution is advised when administering aciclovir to patients with impaired renal function. Adequate fluid intake should be ensured at all times.
In the treatment of herpes simplex infections in patients with severe renal impairment (creatinine clearance less than 10 ml/min), an adjustment of the dosage to 200 mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

Method of administration
Tablets should be taken after meals where possible, and with an adequate quantity of fluids.

To achieve the best possible treatment success, use of the medicinal product should start as early as possible, i.e., after appearance of the first skin

symptoms where possible. In particular with recurrent herpes simplex infections, use of aciclovir should start when the first signs of renewed infection begin (e.g., itching, tightness, initial lesions).

In particular in patients with impaired renal function, as found more commonly in elderly patients, adequate fluid intake should be ensured during treatment.

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

For the prevention of herpes simplex infections in immunocompetent patients, the duration of treatment depends on the severity and frequency of the recurrences. However, this should not exceed a period of 12 months.

The duration of use for the prophylaxis of herpes simplex infections in severely immunocompromised patients is determined based on the severity of the immunosuppression and the duration of the risk of infection and is to be decided by the doctor on a case by case basis.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Adequate fluid intake should be ensured at all times in patients receiving IV aciclovir or those taking high doses of aciclovir.

The risk of renal impairment is increased by use with other nephrotoxic medicinal products. Patients with renal impairment and elderly patients
Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal
impairment (see section 4.2). Elderly patients are likely to have reduced renal function, therefore the need for dose reduction should be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should therefore be closely monitored for signs of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

As there are currently no data on the prophylactic use of aciclovir in patients with impaired renal function or anuria, the products should not be used under these conditions.

Development of resistance
Prolonged or repeated treatment with aciclovir in severely immunocompromised patients may result in the selection of virus strains with reduced sensitivity. These virus strains may not respond to continued

aciclovir treatment.

This medicine contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that are also eliminated via this mechanism may increase the plasma concentration of aciclovir. Cimetidine and probenecid increase the AUC of aciclovir by this mechanism and reduce aciclovir renal clearance. A similar increase in the plasma AUC of aciclovir and the inactive metabolite of mycophenolate mofetil has been shown when the drugs are co-administered.

However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

An experimental study on five male subjects suggests that concomitant therapy with aciclovir increases the AUC of totally administered theophylline by approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

4.6 Fertility, pregnancy and lactation

Fertility
See section 5.3.

Pregnancy
The use of aciclovir during pregnancy should only take place when the potential benefits outweigh the possible risks.

Since marketing authorisation, pregnancy outcomes in women exposed to any formulation of aciclovir have been documented in a pregnancy registry. This shows no increase in the number of birth defects compared with the general population. The birth defects documented showed no uniqueness or consistent pattern to suggest a common cause (see also section 5.3). Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. In a non-standard test, foetal abnormalities were observed but only following subcutaneous doses that were so high that maternal toxicity was produced. The clinical relevance of these results is unclear.

Breast-feeding
Following oral administration of 200 mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels of aciclovir. These levels would expose nursing infants to aciclovir concentrations of up to 0.3 mg/kg/day. Therefore, mothers should not breast-feed during treatment

with aciclovir.

4.7 Effects on ability to drive and use machines

The clinical status of a patient and the adverse effect profile of aciclovir should be considered when determining whether a patient is able to drive a car or use machines.
There have been no studies to investigate the effects on driving performance or the ability to use machines.

4.8 Undesirable effects

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for calculating frequencies are not available. In addition, adverse events may vary in their frequency depending on the indication.

The following convention has been used for the classification of undesirable effects in terms of frequency:

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 (frequency 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 agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, impaired consciousness including coma

The above events are generally reversible and are mainly reported in patients with renal impairment or with other predisposing factors (see section 4.4).

Respiratory, thoracic and mediastinal disorders Rare: dyspnoea

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

Hepatic and biliary disorders
Rare: transient rises in bilirubin and hepatic enzymes Very rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: pruritus, rash (including photosensitivity reactions) Uncommon: urticaria, accelerated diffuse hair loss
As accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship to the use of medicinal products containing aciclovir is unclear.
Rare: angioedema

Renal and urinary disorders
Rare: increases in serum urea and creatinine Very rare: acute renal failure, renal pain
Renal pain may be associated with renal failure

General disorders and administration site conditions Uncommon: fatigue, fever

Reporting of suspected adverse reactions
Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

Symptoms
Aciclovir is only partly absorbed in the gastrointestinal tract.

No toxic effects have generally been observed following the ingestion of single doses of up to 20 g aciclovir. Accidental, repeated overdose of oral aciclovir over several days has been associated with gastrointestinal symptoms (such as nausea and vomiting) and neurological symptoms (headache and confusion).

Overdose of intravenous aciclovir has resulted in elevations of serum creatinine and blood urea nitrogen, and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in connection with such intravenous overdose.

Measures
Patients should be observed for signs of toxicity. Haemodialysis can significantly accelerate the elimination of aciclovir from the blood. Therefore, haemodialysis may be considered in the event of a symptomatic overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties
Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors, ATC code: J05AB01

Mechanism of action
Aciclovir is a pharmacologically inactive substance that only become a virostatic agent after penetration into a cell infected with herpes simplex virus (HSV) or varicella zoster virus (VZV). This activation of aciclovir is catalysed by HSV or VZV thymidine kinase, an enzyme that is crucial to the replication of the viruses.

Simply put, it is possible to say that the virus synthesises its own virostatic. The individual steps are as follows:

1. Aciclovir penetration is increased in cells infected with herpes.
2. The viral thymidine kinase present in these cells phosphorylates aciclovir to aciclovir monophosphate.
3. Cellular enzymes convert aciclovir monophosphate into the actual virostatic aciclovir triphosphate.
4. The affinity of aciclovir to viral DNA polymerase is between 10 and 30 times higher than its affinity to cellular DNA polymerase, and in this way it selectively inhibits the activity of the viral enzyme.
5. The viral DNA polymerase also incorporates aciclovir into the viral DNA, resulting in chain termination in the DNA synthesis. Overall, these individual steps result in a very effective reduction in virus production.

In the plaque-reduction neutralization test, an ED50 inhibitory value of 0.1 µmol aciclovir/l was measured for HSV-infected vero cells (cell cultures from the renal parenchyma of the African green monkey), while in contrast an ED50 value of 300 µmol aciclovir/l was required to prevent growth in non-infected vero cell cultures.
As such, aciclovir concentrations in non-infected cell cultures need to be 3,000 times higher in order to achieve equivalent inhibition.

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

5.2 Pharmacokinetic properties

Absorption, plasma levels
Aciclovir is only partly absorbed from the gastrointestinal tract. Mean steady

state peak plasma concentrations following repeated oral administration of 200 mg, 400 mg and 800 mg aciclovir five times daily at four-hourly intervals were 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). These values are achieved after approx. 1.5 ± 0.6 hours. The corresponding trough plasma levels approximately 4 hours after oral administration of aciclovir are
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). Aciclovir is no longer detectable in the body 24 hours after discontinuation of aciclovir tablets.

In immunocompromised children aged 3-11 years given oral aciclovir 5 times daily at doses of
400 mg, corresponding to 300-650 mg aciclovir/m^2 BSA, mean peak plasma levels of 5.7-15.1 µmol/l were measured.

In infants aged between 1 and 6 weeks, peak plasma levels of 17.3 or 8.6 µmol/l were measured following oral administration of 600 mg aciclovir/m^2 BSA every 6 hours.

In neonates and infants up to 3 months given 10 mg/kg aciclovir as a 1-hour infusion every 8 hours, a C_{max} of 61.2 µmol/l (13.8 µg/ml) and a C_{min} of 10.1 µmol/l (2.3 µg/ml) were measured. Another group of neonates and infants (up to 3 months) given 15 mg/kg aciclovir every 8 hours showed roughly dose-proportionate increases, with a C_{max} of 83.5 µmol/l (18.8 µg/ml) and a C_{min} of 14.1 µmol/l (3.2 µg/ml).

Given the biexponential course of aciclovir kinetics, it is possible to conclude that aciclovir reaches the tissues and organs in high concentrations, and that this concentration then slowly recedes.

The volume of distribution in steady state in adults is 50 ± 8.7 l/1.73 m^2 and 28 ± 9.3 l/1.73 m^2 in neonates and infants up to 3 months.
Values between 9 and 33% have been measured for
protein binding. <u>Distribution in the organs</u>
Animal studies have shown that aciclovir levels in the intestinal tract, kidney, liver and lungs are
higher than those found in serum, while lower levels are found in muscle tissue and in the heart, brain, ovaries and testes of the animals.

Post-mortem examinations in humans showed that aciclovir accumulates in saliva, vaginal secretions, and in the vesicular fluid of herpes blisters, as well as in some organs. Cerebrospinal fluid levels are approximately 50% of corresponding serum levels.

<u>Metabolism and elimination</u>
In patients with healthy kidneys, 62-91% of the aciclovir administered is eliminated via the kidneys in unchanged form, and 10-15% is eliminated as 9-carboxymethoxymethylguanine. Plasma half-lives ($t_{1/2\beta}$) of 2.87 ± 0.76 hours have been measured in adults and 4.1 ± 1.2 hours in neonates and children up to 3 months. Tubular secretion and glomerular filtration contribute to the renal elimination of aciclovir. When aciclovir is given one

hour after the administration of 1 g of probenecid, the plasma half-life ($t_{1/2\beta}$) is extended by 18%, and the area under the plasma concentration time curve is increased by 40%. Aciclovir and its metabolites are not eliminated via the bile or faeces.

In patients with chronic renal failure, the mean plasma half-life is approximately 19.5 hours. The mean plasma half-life during haemodialysis is 5.7 hours. Plasma aciclovir levels drop by approximately 60% during haemodialysis. With impaired renal function there is a risk of accumulation at a dosage of 200 mg five times daily if creatinine clearance values are <10 ml/min/1.73 m^2. Therefore a dose reduction is indicated below this value (see section 4.2).

5.3 Preclinical safety data

Acute toxicity
It was not possible to determine the LD50 value with the oral administration of aciclovir to mice and rats, and doses of more than 10 g/kg in mice and 20 g/kg in rats could not be exceeded for physiological reasons, and the animals survived these doses.

Chronic toxicity
Up to 450 mg aciclovir/kg was administered to mice via oral route for 4 weeks. All animals survived and showed no anomalies.

In a 12-month study, beagle dogs were given up to 60 mg aciclovir/kg/day via oral route. Mucus diarrhoea and vomiting occurred commonly at this dose. Pad alterations and claw loss were observed in some dogs. These events were, however, reversible. No other abnormalities were observed.

Rats and mice were given up to 450 mg aciclovir/kg daily over a period of 775 days, and no alterations were observed.

Mutagenic and carcinogenic potential
In vitro tests showed that chromosomal damage may occur at high concentrations. In one in vivo study in the Chinese hamster, chromosomal damage was observed at toxic doses. In view of the low concentrations occurring in germ cells, germ cell damage is not to be expected with therapeutic use.

Aciclovir was not found to be carcinogenic in long-term studies on rats and mice. Reproductive toxicity
Systemic exposure to aciclovir in internationally accepted standard tests did not produce embryotoxic
or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is unclear.

Fertility
Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of

aciclovir greatly in excess of those employed therapeutically.

Two generation studies in mice did not reveal any effects on fertility with oral administration of aciclovir (up to 450 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline
cellulose Sodium
starch glycolate
Povidone K25
Colloidal anhydrous silica
Magnesium stearate
[vegetable] Maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

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

10179

9. DATE OF FIRST AUTHORISATION IN GERMANY

29/05/1995

10. DATE OF REVISION OF THE TEXT

06/2023

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription