Supraviran® 250 mg i.v.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Supraviran® 250 mg i.v.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial with 274.4 mg powder for the preparation of an infusion solution contains 274.4 mg Aciclovir sodium, equivalent to 250 mg Aciclovir.
Excipients: none.

3. PHARMACEUTICAL FORM
Powder for the preparation of an infusion solution

4. CLINICAL PARTICULARS

4.1 Indications
Primary genital herpes and infections of the skin and mucous membranes caused by herpes simplex viruses in patients with in-born weak immunity or those with secondary immune defects, which might occur during immunosuppressant (e.g. after or organ transplantation) or cytostatic treatment.

4.2 Dosage, Mode and Duration of Administration
Obese adults should receive the recommended adult dose on the basis of the ideal weight and less than on the basis of the actual weight.
Adults and children from the age of 12 years and neonates and infants up to three months
Neonates, infants up to the age of three months, children from the age of 12 years and adults receive the same dosage related to kg body weight.

Children from the age of three months to 12 years

Children from the age of three months to 12 years receive Supraviran® 250 mg i.v. in relation to their body surface in order to avoid underdosing.

For further details see tables 1 and 2.

Table 1
Neonates, infants up to the age of three months, children from the age of 12 years and adults receive the intravenous infusion according to the following dosage regimen:

Patients with a normal immune system

Indications	Single dose (mg/kg bw) Aciclovir	Mean duration of treatment (in days)	Daily dose on normal renal function (mg/kg bw)
Primary genital herpes	5	5 *	15

Patients with immune defects

Herpes simplex infections	5	5 *	15

* Treatment may be longer in some cases and depends on the patient's clinical condition.

Table 2
Children from the age of three months up to 12 years receive the intravenous infusion according to the following dosage:

Patients with a normal immune system

Indications	Single dose mg Aciclovir/m²	Mean duration of treatment (in days)	Daily dose on normal kidney function mg Aciclovir/m²
Primary genital herpes	250	5 *	750

Patients with immune defects

Herpes simplex infections	250	5 *	750

* Treatment may be longer in some cases and depends on the patient's clinical condition.
Patients with normal renal function receive the single dose three times daily every eight hours.
Dosage on renal function disorders
For information on the dosage in patients with impaired renal function see table 3.

Table 3
Patients with impaired renal function receive a single dose according to the following regimen:

Creatinine clearance (ml/min/1.73 m²)	Serum creatinine (µmol/l / mg/dl) Women	Men	Dosage interval of the single doses
> 50	< 130 / < 1.47	< 170 / < 1.92	every 8 hours
50 - 25	130-280 / 1.47-3.17	170-370 / 1.92-4.18	every 12 hours
25 - 10	280-550 / 3.17-6.22	370-750 / 4.18-8.48	every 24 hours
10 - 0 (anuric)	> 550 / > 6.22	> 750 / > 8.48	Half a single dose every 24 hours in CAPD* or after each haemodialysis

* CAPD: continuous ambulatory peritoneal dialysis

Elderly patients
Since elderly patients in particular have an increased incidence of impaired renal function, this should be monitored in this patient group and attention paid that they receive a reasonable amount of fluid. If necessary, the dose is to be adjusted according to the regimen shown in Tab. 3.

Higher dosages
If high doses of Aciclovir are given, renal function should also be monitored. This applies particularly to patients with restricted kidney function and those who drink little fluid.

Mode of Administration
Preparation of the infusion solution
The contents of one vial are to be dissolved by adding 10 ml water for injections or physiological saline solution. This concentrated solution, or parts of it, are to be added immediately to at least 50 ml (max. 250 ml) solution for infusion.
The concentrated solution has a pH value of approx. 11 and therefore it must not be applied orally.
The ready-to-use solution for infusion is to be prepared under sterile conditions, preferably shortly before administration.
If Supraviran® 250 mg i.v. is to be given intravenously by means of an infusion pump, solutions containing up to 2.5% Aciclovir (25 mg Aciclovir) should be used.
Physiological saline solution is recommended as the infusion solution and must not contain any additives, apart from Supraviran® 250 mg i.v.. Any unused remains of the powder for preparation of an infusion solution or the concentrated solution must be discarded.
After addition of Supraviran® 250 mg i.v., ready-to-use solutions for infusion may be stored for up to 12 hours at +15°C to +25°C. ***Solutions for infusion must on no account be stored in a refrigerator.***

If the ready-to-use solution becomes turbid or precipitates before or during infusion, the infusion must be terminated and the solution for infusion discarded.
Supraviran® 250 mg i.v. must be given as an intravenous infusion, not as a bolus injection.
Each single dose should be infused slowly over a period of one hour.

4.3 Contraindications
Hypersensitivity towards medicinal products containing Aciclovir or valAciclovir.

4.4 Precautions and Warnings
None

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction
No clinically significant interactions have so far been observed.
Aciclovir is mainly excreted unchanged via the kidneys in the urine by means of active tubular secretion. Medicines given concomitantly that are also excreted via this mechanism may increase the plasma concentration of Aciclovir.
Probenecid and cimetidine reduce the renal excretion of Aciclovir by about 30% and 20% respectively, possibly increasing the mean elimination half-life of Aciclovir. In view of the great therapeutic range of Aciclovir dose adjustment is not necessary.

In patients receiving Supraviran® 250 mg i.v. it is possible that on the concomitant administration of active substances that compete with Aciclovir in elimination the plasma levels of one or both substances or their metabolites may be elevated. On concomitant administration of Aciclovir and an inactive metabolite of mycophenolate mofetil, an immunosuppressant used in transplant patients an increase in the plasma AUC has been observed.
Care is necessary (monitoring of renal function) when Supraviran® 250 mg i.v. is administered with active substances that affect renal physiology (e.g. ciclosporin and tacrolimus).

4.6 Pregnancy and Lactation

Very little experience is available on the intravenous administration of Supraviran® 250 mg during pregnancy in humans. Limited experience on the oral administration of Aciclovir during pregnancy does not indicate any side effects of Aciclovir on pregnancy or the health of the foetus/neonate. So far no other relevant epidemiological data are available. Animal experiments have revealed reproduction toxicity (see 13.2). Supraviran® 250 mg i.v. should only be used in pregnancy after careful consideration of the benefit/risk ratio. This applies particularly to use in the first three months of pregnancy.
If intravenous administration of Supraviran® 250 mg i.v. is necessary during pregnancy, care should be taken to see that the single and daily dosages given in section 10 are not exceeded.
Aciclovir passes into the breast-milk. After oral administration the milk : plasma ratio was 4 : 1. As side effects on the breast-fed child cannot be ruled out, breast-feeding should not be carried out during treatment with Supraviran® 250 mg i.v..

4.7 Effects on Ability to Drive and Operate Machinery

Even when used according to instructions this medicine may alter reactions, e.g. due to neurological symptoms (see also section 4.8 Side effects), to such an extent that the ability to drive vehicles, operate machinery or work without a firm hold is impaired. This applies particularly at the start of treatment, on raising the dose, switching the preparation and in connection with alcohol.

4.8 Side effects

After intravenous administration of Supraviran® 250 mg i.v. nausea and vomiting may occur.
There have been reports of reduced haematological parameters (anaemia, thrombocytopenia, leukocytopenia) and reversible elevated bilirubin and liver enzyme values. There have been isolated reports of hepatitis and jaundice.
Hypersensitivity reactions such as rash, including photosensitivity reactions, urticaria, pruritus and fever up to very rare cases of respiratory complaints, angioneurotic oedema and anaphylactic reactions.
After accidental administration of Aciclovir into the perivenous tissues, severe dermatitis - and occasionally necrosis of the affected areas - have been observed.
A transient increase in blood urea and creatinine has occasionally been observed. Presumably this increase is associated with the peak plasma concentration and the patient's hydration status. To avoid this, the preparation should be given in a slow infusion over a period of about an hour and not as an intravenous bolus injection.
Sufficient fluid should be drunk. In the event of kidney function disorders (which in exceptional cases may lead to acute kidney failure) the patient should be rehydrated and/or the dose reduced or the preparation discontinued.
In connection with the intravenous administration of Supraviran® 250 mg i.v., there have been reports of reversible neurological manifestations such as confusion, hallucinations, restlessness, tremor, drowsiness, psychoses, convulsions and coma, mainly in patients suffering from complications.

4.9 Overdose

Symptoms of intoxication
An overdose of intravenous Aciclovir raised serum creatinine and blood urea nitrogen, subsequently leading to renal failure.
Neurological effects including confusion, hallucinations, agitation, convulsions and coma have been reported in connection with this intravenous overdose.
Treatment of intoxication
A four-hour haemodialysis reduces the Aciclovir plasma concentration by 50%. This is triple the clearance. Therefore haemodialysis can be considered in the event of a symptomatic overdose, as well as immediate diuresis with alkalisation of the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: virustatic agent
ATC code: J05AB01
Aciclovir is a pharmacologically inactive substance that only becomes virustatic after penetration into a cell infected with herpes simplex (HSV) or varicella zoster viruses (VZV). The activation of Aciclovir is catalysed by HSV or VZV

thymidine kinase, an enzyme essential for viral replication. In simple terms, the virus synthesises its own virustatic agent. The process is as follows:

1. Aciclovir 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 the actual virustatic substance, Aciclovir triphosphate.
4. The affinity of Aciclovir triphosphate for viral DNA polymerase is 10-30 times greater than for cellular DNA polymerase, thus selectively inhibiting the activity of the viral enzyme.
5. The viral DNA polymerase also incorporates Aciclovir into the viral DNA, resulting in a break in the chain of DNA synthesis.

All these steps very effectively diminish virus production.
In the plaque-reduction test an ED_{50} inhibitory value of 0.1 µmol Aciclovir/l was measured for HSV-infected vero-cells (cell culture from the renal parenchyma of the African green monkey), whereas an ED_{50} value of 300 µmol Aciclovir/l was necessary in order to prevent the growth of non-infected vero-cell cultures. Thus therapeutic indices of up to 3000 were determined for cell cultures.

Spectrum of action in vitro
Very sensitive: Herpes simplex virus type I and II, varicella zoster virus
Sensitive: Epstein-Barr virus
Partially sensitive to resistant: Cytomegalovirus

Resistant
RNA viruses, adenoviruses, pox viruses.
In severely immunosuppressed patients long-term or repeated treatment with Aciclovir may lead to selection of viral strains with reduced sensitivity with the result that these patients may no longer respond to Aciclovir treatment.
Most of the clinical isolates with reduced sensitivity were relatively deficient in viral thymidine kinase. However, there have also been reports of modified viral thymidine kinase and DNA polymerase. In-vitro exposure of HSV isolates to Aciclovir may also lead to the development of less sensitive strains. The connection between in-vitro sensitivity of HSV isolates and clinical response to treatment with Aciclovir is unclear.

5.2 Pharmacokinetic Properties

After a one-hour infusion of 5 mg/kg body weight in adults a mean plasma peak of 33.7 ± 7.08 µmol/l was measured, after an infusion of 10 mg/kg body weight 51.6 ± 2.7 µmol/l. Seven hours later (before the next infusion) mean basal values of 4.11 ± 0.75 µmol/l and 6.4 µmol/l were determined. These values did not change even after multiple administration (steady-state)
After administration of 250 mg and 500 mg Aciclovir/m² body surface in children up to the age of 12 years, the plasma peak and basal values are almost identical to those obtained in adults after administration of 5 mg and 10 mg Aciclovir per kg.
In neonates and infants up to the age of three months given 5 mg and 10 mg acíclovir per kg (in a one-hour infusion every eight hours) plasma peak values of 30.0 ± 9.9 µmol/l and 61.2 ± 18.3 µmol/l. Plasma basal values were 5.3 ± 3.4 µmol (with 5 mg/kg) and 10.1 ± 8.4 µmol/l (with 10 mg/kg Aciclovir).
The bi-exponential curve of Aciclovir kinetics shows that high concentrations of Aciclovir pass into the tissues and organs and slowly return to the systemic circulation.
The steady-state distribution volume is 50 ± 8.7 l/1.73 m² in adults, and 28.8 ± 9.3 l/1.73 m² in neonates and infants up to the age of three months.
Protein-binding ranged between 9% and 33%.
Organ distribution
Animal experiments have shown that in comparison with the plasma levels higher Aciclovir levels are attained in the intestines, kidneys, liver and lungs, and lower levels in the muscles, heart, brain, ovaries and testes.
Post-mortem examinations in humans showed that Aciclovir accumulates in the saliva, vaginal secretion, the fluid of herpetic vesicles and in some organs. 50% of the corresponding serum concentrations are attained in the cerebrospinal fluid.
Metabolism and elimination
62-91% of Aciclovir is eliminated unchanged via the kidneys in patients with healthy kidneys and 10-15% as 9-carboxymethoxymethylguanine. Plasma half-lives ($t_{½ß}$) of 2.87 ± 0.76 h were measured in adults and 4.1 ± 1.2 h in neonates and infants up to three months. Aciclovir is filtered in the glomerules and excreted via the tubules. If Aciclovir is given one hour after administration of 1 g probenecid, the plasma half-life ($t_{½ß}$) is prolonged by 18% and the area under the plasma concentration curve extended by 40%. Aciclovir and its metabolites are not excreted in the bile or faeces.
In patients with chronic renal insufficiency the mean plasma half-life is approx. 19.5 h. The mean plasma half-life during haemodialysis is 5.7 h. During haemodialysis Aciclovir plasma levels decrease by about 60%. In impaired renal function there is a risk of accumulation with creatinine clearance values of < 50 ml/min. Therefore the dose should be reduced in cases below this value (see also section 10 Dosage).
Bioavailability
100 %

5.3 Preclinical Safety Data

Rats were given i.v. bolus injections of 5, 10, 20, 40 and 80 mg Aciclovir/day for 20 days. With doses above 10 mg elevated serum concentrations and precipitations of Aciclovir in the distal tubules were observed. After administration of the highest dose some animals exhibited a slightly raised leukocyte count.
Beagles were given daily doses of 0, 20, 50, 100 and 200 mg/kg, divided up into two injections per day for 31 days. In the 50 mg group urine production was raised and isolated cases of retching, tachycardia, hyaline inclusions in the cytoplasm of the liver cells, changes in the intestinal mucosa and the renal parenchyma, and tubular damage. In the 100 mg and 200 mg groups bloody mucid stools, pathological changes in liver enzymes, leukopenia, hypoplasia of the bone marrow and lymph tissue, tremor and cyanosis were observed. All the dogs treated with the highest dose of 200 mg/kg/day died within eight days.
In-vitro and in-vivo tests on genetic toxicology with Aciclovir revealed negative and positive results. However, positive effects only occurred with very high concentrations, which in some cases were cytotoxic. Under clinical conditions a relevant genotoxic potential is improbable.
In long-term studies in rats and mice Aciclovir was not carcinogenic.
For the most part reversible detrimental effects on spermatogenesis in rats and beagles only occurred after administration of Aciclovir doses far above the normal therapeutic range. Investigations over two generations of mice showed no effects of oral Aciclovir whatsoever on fertility. Oral Aciclovir in men had no effects on sperm count, morphology or motility.

Embryotoxicity studies on subcutaneous administration of Aciclovir in rats or intravenous and subcutaneous administration in rabbits showed no embryotoxic or teratogenic effects. In another study high subcutaneous doses in rats produced teratogenic effects (anophthalmia and tail anomalies) on individual days during embryonal development. The effects occurred in the maternally toxic dose range and with Aciclovir plasma concentrations far above the therapeutic plasma concentrations. The clinical relevance of this study is therefore doubtful.

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients

None

6.2 Incompatibilities

Acid or buffered infusion solutions are incompatible.

6.3 Shelf-life

4 years

6.4 Special Precautions for Storage

None

6.5 Nature and Contents of Container

Pack of 10 vials each with 274.4 mg powder for the preparation of an infusion solution.

6.6 Instructions for Use and Handling

Any infusion solution prepared more than 12 hours previously must not be used.
Any remains of the powder for preparation of an infusion solution or the concentrated solution must be discarded.

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

June 2005

9. LEGAL CATEGORY

Prescription-only