SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Supraviran® 200 mg
Supraviran® 400 mg
Supraviran® 800 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One Supraviran® 200 mg tablet contains 200 mg aciclovir.
One Supraviran® 400 mg tablet contains 400 mg aciclovir.
One Supraviran® 800 mg tablet contains 800 mg aciclovir.
Excipients: see Section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Indications

Supraviran® 200 mg
Herpes simplex, in particular *herpes genitalis infections* of the skin and mucous membranes (first and recurrent infections in the genital region)
Attempted prophylaxis in adults suffering from very severe forms of recurrent genital *herpes simplex infections* is indicated.

Supraviran® 400 mg
Herpes zoster (shingles) Prophylaxis of severe herpes simplex infections in severely immunocompromised adult patients in times of increased risk of infection, e.g. after organ transplantation

Supraviran® 800 mg
Herpes zoster (shingles)

4.2 Dosage, Mode and Duration of Administration

Adults
Herpes zoster (shingles)
A single dose of 800 mg aciclovir, equivalent to two Supraviran® 400 mg tablets or one Supraviran® 800 mg tablet five times during the day at intervals of four hours. In severely immunosuppressed patients or patients with impaired enteral absorption the administration of aciclovir for intravenous infusion should be considered.
Herpes simplex infections
A single dose of 200 mg aciclovir (one Supraviran® 200 mg tablet) five times during the day at intervals of four hours.
In severely immunosuppressed patients or patients with impaired absorption the administration of aciclovir for intravenous infusion should be considered.
Prophylaxis of severe forms and recurrent genital herpes simplex infections
Patients with normal immune response receive a single dose of 200 mg aciclovir (one Supraviran® 200 mg tablet) four times daily at intervals of six hours. Alternatively, 400 mg aciclovir (two Supraviran® 200 mg tablets or one Supraviran® 400 mg tablet) can be given twice daily at intervals of 12 hours. In some cases effective prophylaxis can also be obtained with a dose of 200 mg aciclovir three times daily at intervals of eight hours or 200 mg aciclovir twice daily at intervals of 12 hours.
If there is a recurrence despite the total daily dose of 800 mg, 200 mg aciclovir five times during the day every four hours are to be given for five days - as in the dosage for *herpes simplex infections*. Afterwards the above-mentioned dosage is to be resumed.
Immunosuppressed patients receive a single dose of 200 mg aciclovir (one Supraviran® 200 mg tablet) four times daily at intervals of six hours for prophylaxis.
Severely immunosuppressed patients, e.g. after organ transplantation, may be given a single dose of 400 mg aciclovir (two Supraviran 200 mg tablets or one Supraviran 400 mg tablet) four times daily at intervals of six hours. Alternatively, aciclovir for intravenous infusion can be given - particularly in patients with impaired enteral absorption.
Note:
Trends of possible resistance have been reported in immunosuppressed patients. This should be borne in mind when fixing the dose.

Children
For the treatment of *herpes simplex infections* children above the age of two years receive the adult dose and children below two years half the adult dose.

Patients with renal insufficiency (see section 4.3)
In patients with impaired renal function a lower dose of aciclovir, as given below, may suffice. If necessary, the physician will adjust the dose, depending on the renal function values (see table).

Indication	Cl_{cr} **(ml/min/1.73 m²)**	**Serum creatinine (µmol/l / mg/dl)** **Women**	**Men**	**Single dose**
Herpes simplex infections	**< 10**	**> 550/ > 6.22**	**> 750 > 8.48**	**200 mg aciclovir twice daily every 12 hours**
Herpes zoster	**25 - 10**	**280-550/ 3.17-6.22**	**370-750/ 4.18-8.48**	**800 mg aciclovir three times daily every 8 hours**
	< 10	**> 550/ > 6.22**	**> 750/ > 8.48**	**800 mg aciclovir twice daily every 12 hours**

Elderly patients
In elderly patients the total clearance of aciclovir decreases in line with Cl_{cr}. In elderly patients taking high doses of Supraviran® tablets, attention is to be paid that they drink a reasonable amount of fluid.
In elderly patients with impaired renal function special attention should be paid to reducing the dose.

Mode of Administration
If possible, the tablets should be taken with liquid after meals.
Particularly in cases of impaired renal function, especially in elderly patients, care should be taken to see that sufficient fluid is drunk during treatment.
Supraviran® tablets should be taken as soon as possible after the appearance of the first signs of an infection. Particularly in recurrent *herpes simplex infections* Supraviran® tablets should be taken at the first signs of renewed infection (e.g pruritus, feeling of tension, early vesicles). Investigations have shown that early treatment of *herpes zoster* with a preparation containing aciclovir has a beneficial effect on the symptoms.

Duration of administration
In *herpes zoster* the duration of treatment is 5-7 days.
In *herpes simplex infections* the duration of treatment is five days, but it may be prolonged, depending on the patient's clinical condition.
In the prophylaxis of *herpes simplex infections* in patients with a normal immune response the duration of treatment depends on the severity of the disease and frequency of recurrences. However, a period of 6-12 months should not be exceeded.
The duration of treatment in the prophylaxis of *herpes simplex infections* in severely immunosuppressed patients depends on the severity of immunosuppression and the duration of the risk of infection.

4.3 Contraindications
Hypersensitivity towards preparations containing aciclovir or valaciclovir or one of the other ingredients.
As no reports are available on prophylactic treatment with Supraviran® 200 mg and 400 mg in patients with impaired renal function or anuria, the preparations should not be used in these circumstances.
Supraviran® 800 mg
Supraviran® 800 mg is not suitable for the treatment of children.

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 acyclovir.
Cimetidine and probenecid reduce the renal excretion of aciclovir by about 20% and 30% respectively, possibly increasing the mean elimination half-life of aciclovir.
On concomitant administration of aciclovir and an inactive metabolite of mycophenolate mofetil, an immunosuppressant used in transplant patients a similar increase in the plasma AUC has been observed.
In view of the great therapeutic range of aciclovir dose adjustment is not necessary.
In patients with given antiretroviral treatment mainly orally (zidovudine) the additional administration of a medicine containing aciclovir is not associated with a significant increase in toxicity.

4.6 Pregnancy and Lactation
Limited experience on the oral administration of aciclovir during pregnancy do not indicate any side-effects of aciclovir on pregnancy or the health of the foetus/neonate. So far no relevant epidemiological data are available. Animal experiments have revealed reproduction toxicity (see 13.2). Aciclovir should only be used in pregnancy after careful consideration of the benefit/risk ratio.

Aciclovir passes into the breast milk (milk : plasma ratio 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 200 mg/400 mg/800 mg.

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 administration of Supraviran tablets the following side-effects have occasionally been observed. There have been reports of gastrointestinal disorders such as nausea, vomiting, diarrhoea and abdominal pain.
Hypersensitivity reactions such as rash, including photosensitivity reactions, urticaria and pruritus up to rare cases of respiratory complaints, angioneurotic oedema and anaphylactic reactions.
Neurological manifestations have also occurred occasionally. Particularly in patients with impaired renal function given doses above those recommended or with other diseases that may promote the following effects there have been reports of reversible neurological reactions, in particular dizziness, confusion, hallucinations, drowsiness and seizures. Also predominantly in such patients there have been isolated cases of symptoms of psychoses and consciousness disorders up to coma.
Headache, listlessness, insomnia and tiredness have been observed on rare occasions. Moreover, in isolated cases feelings of estrangement, which disappeared after discontinuation of the medicine, have also been observed. There have been rare reports of transient elevated bilirubin, liver enzyme, serum urea and creatinine values. On very rare occasions anaemia, leukopenia and thrombocytopenia have occurred. There have been isolated reports of acute renal failure, hepatitis and jaundice.
There have also been occasional reports of loss of hair (diffuse alopecia), but it is not certain whether this was connected with the administration of medicines containing aciclovir.

4.9 Overdose
Aciclovir is only partly absorbed from the gastrointestinal tract (see also section 5.2 *Bioavailability*).
Symptoms
After administration of single doses of up to 20 g aciclovir in general no toxic effects occurred. Accidental repeated overdoses of oral aciclovir for several days were associated with gastrointestinal symptoms (such as nausea and vomiting) and neurological symptoms (headache and confusion).
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.
Actions
Patients should be monitored for signs of toxicity. A four-hour haemodialysis reduces the aciclovir plasma concentration by 50%. This is triple the clearance. Therefore haemodialysis may be considered in the event of a symptomatic overdose.

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

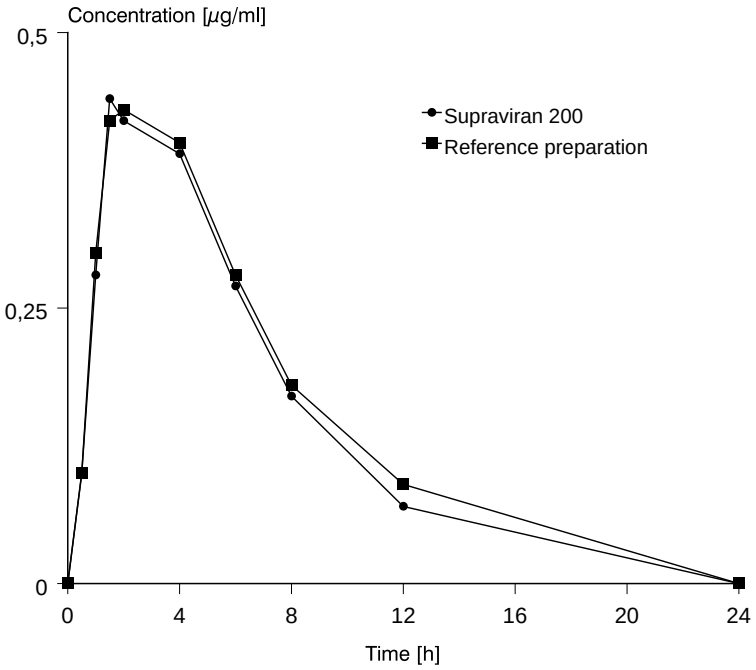
5.2 Pharmacokinetic Properties

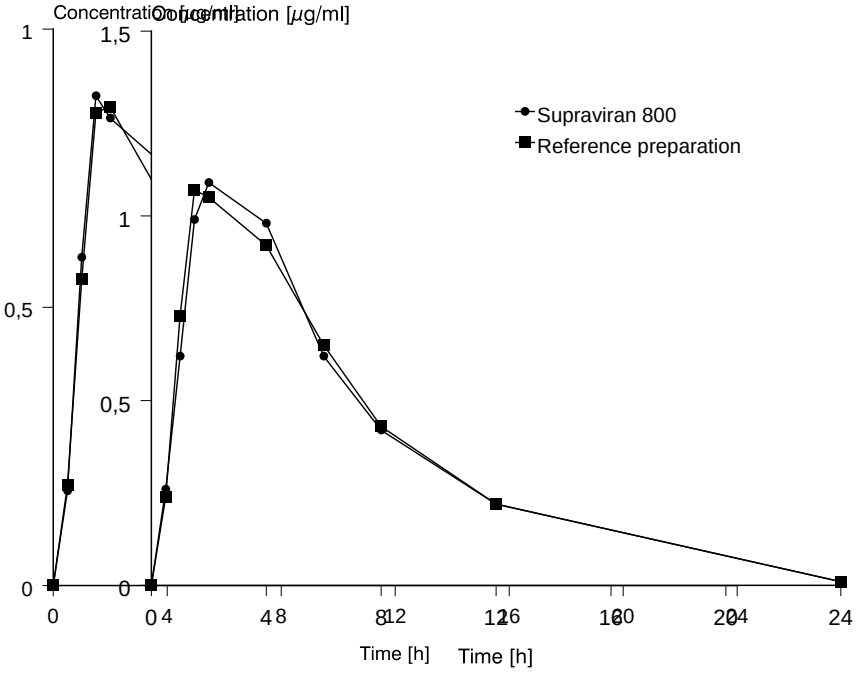
Aciclovir is only partially absorbed from the gastrointestinal tract. The mean steady-state plasma peaks after repeated oral administration of 200 mg, 400 mg and 800 mg aciclovir five times daily every four hours were 3.02 ± 0.5 µmol/l (200 mg), 5.21 ± 1.32 µmol/l (400 mg) and 8.16 ± 1.98 µmol/l (800 mg) respectively.
These values are reached after about 1.5 ± 0.6 hours. The corresponding plasma basal values about four hours after oral administration of aciclovir were 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) respectively. Twenty-four hours after discontinuation of the drug containing aciclovir (400 mg), the substance was no longer detectable in the body.
In immunosuppressed children aged 3-11 years given aciclovir orally in doses of 400 mg, equivalent to 300-650 mg aciclovir/m² body surface, five times daily, mean plasma peaks of 5-7 - 15.1 µmol/l were determined. In infants aged 1-6 weeks plasma peaks of 17.3 and 8.6 µmol were measured after oral administration of 600 mg aciclovir/m² body surface every six hours.
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 serum 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. After i.v. administration of aciclovir plasma half-lives ($t_{½ß}$) of 2.87 ± 0.76 hours were determined in adults and 4.1 ± 1.2 hours in neonates and infants up to the age of 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%. With a bioavailability of about 20% approx. 80% of the total dose of aciclovir is excreted in the 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 cases of impaired renal function there is a risk of accumulation with Cl_{cr} values of < 25 ml/min/1.73 m² (with a dose of five times 800 mg/day). Therefore the dose should be reduced in cases below this value (see also section 10, *Dosage*).

Bioavailability
The bioavailability of oral aciclovir is about 20% of the administered dose.
A bioavailability study carried out on 20 volunteers in 1992 showed the following results compared with the reference preparation:

	Supra-viran 200 mg	**Reference preparation**	**Supra-viran 400 mg**	**Reference preparation**	**Supra-viran 800 mg**	**Reference preparation**
Peak plasma concentration C_{max} (µg/ml)	0.47 ± 0.16	0.45 ± 0.15	0.89 ± 0.4	0.95 ± 0.41	1.21 ± 0.42	1.17 ± 0.47
Time of peak plasma concentration t_{max} (h)	2.28 ± 1.06	2.13 ± 1.02	1.63 ± 0.32	1.68 ± 0.29	1.95 ± 0.74	1.68 ± 0.29
Area under the concentration/time curve AUC (µg/ml.h)	3.27 ± 1.04	3.56 ± 1.36	6.71 ± 3.62	6.52 ± 3.21	8.26 ± 3.51	8.20 ± 3.40

(Mean values with standard deviation)
The figure shows the mean plasma concentration compared with the reference preparation (n = 20) in a concentration/time diagram:





5.3 Preclinical Safety Data

Up to 450 mg aciclovir/kg orally were given to mice over a period of four weeks. All the animals survived and did not exhibit any anomalies.
In a 12-month study beagles were given up to 60 mg aciclovir/kg/day orally. With this dose the incidence of mucid diarrhoea and vomiting was raised. In some dogs there were changes in their paws and loss of claws. However, these manifestations were reversible. No other abnormalities were observed.
Rats and mice were given up to 450 mg aciclovir/kg for a period of 775 days without any changes being observed.
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

Supraviran® 200 mg, Supraviran® 400 mg, Supraviran® 800 mg
Sodium carboxymethylcellulose, copovidone; magnesium stearate (Ph. Eur.); colloidal anhydrous silica; microcrystalline cellulose

6.2 Incompatibilities

None known so far.

6.3 Shelf-life

4 years

6.4 Special Precautions for Storage

None

6.5 Nature and Contents of Container

Supraviran® 200 mg:	Original pack with 25 tablets
Supraviran® 400 mg:	Original pack with 35 tablets
Supraviran® 800 mg:	Original pack with 35 tablets

6.6 Instructions for Use and Handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF REVISION OF THE TEXT

June 2005

9. LEGAL CATEGORY

Prescription-only