Zovirax
Aciclovir
Oral Formulation

QUALITATIVE AND QUANTITATIVE COMPOSITION
Tablets containing 200 mg aciclovir.

CLINICAL INFORMATION
Indications
ZOVIRAX oral formulations are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.

ZOVIRAX oral formulations are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immune-competent patients.

ZOVIRAX oral formulations are indicated for the prophylaxis of herpes simplex infections in immune-compromised patients.

ZOVIRAX oral formulations are indicated for the treatment of varicella infections (chicken-pox) and herpes zoster (shingles).

Dosage and Administration
Pharmaceutical form
Tablets.

Adults
Treatment of herpes simplex
For treatment of herpes simplex infections, 200 mg *ZOVIRAX* should be taken five times daily at approximately four-hourly intervals omitting the night time dose. Treatment should continue for five days but in severe initial infections may have to be extended.

In severely immune-compromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg or, alternatively, intravenous dosing could be considered.

Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.

Suppression of herpes simplex
For suppression of herpes simplex infections in immune-competent patients, 200 mg *ZOVIRAX* should be taken four times daily at approximately six-hourly intervals.

Many patients may be conveniently managed on a regimen of 400 mg *ZOVIRAX* taken twice daily at approximately twelve-hourly intervals.

Dosage titration down to 200 mg *ZOVIRAX* taken thrice daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.

Some patients may experience break-through infections on total daily doses of 800 mg *ZOVIRAX*.

Therapy should be interrupted periodically at intervals of six to twelve months in order to observe possible changes in the natural history of the disease.

Prophylaxis of herpes simplex
For prophylaxis of herpes simplex infections in immune-compromised patients, 200 mg *ZOVIRAX* should be taken four times daily at approximately six-hourly intervals.

In severely immune-compromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg or, alternatively, intravenous dosing could be considered.

The duration of prophylactic administration is determined by the duration of the period at risk.

Treatment of varicella and herpes zoster
For treatment of varicella and herpes zoster infections, 800 mg *ZOVIRAX* should be taken five times daily at approximately four-hourly intervals, omitting the night time dose. Treatment should continue for seven days.

In severely immune-compromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.

Dosing should begin as early as possible after the start of an infection. Treatment yields better results if initiated as soon as possible after onset of the rash.

Children
For treatment of herpes simplex infections, and for prophylaxis of herpes simplex infections in the immune-compromised, children aged two years and over should be given adult dosages and children below the age of two years should be given half the adult dose.

For treatment of varicella infections in children:

6 years and over:	800 mg *ZOVIRAX* four times daily
2 - <6 years:	400 mg *ZOVIRAX* four times daily
Under 2 years:	200 mg *ZOVIRAX* four times daily

Dosing may be more accurately calculated as 20 mg *ZOVIRAX*/kg body weight (not to exceed 800 mg) four times daily. Treatment should continue for five days.

No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immune-competent children.

Elderly
The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (*see Renal impairment*).

Adequate hydration of elderly patients taking high oral doses of *ZOVIRAX* should be maintained.

Renal impairment
Caution is advised when administering *ZOVIRAX* oral formulations to patients with impaired renal function. Adequate hydration should be maintained.

In the treatment and prophylaxis of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established safe by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 mL/minute) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of varicella and herpes zoster infections, it is recommended to adjust the dosage to 800 mg twice daily, at approximately twelve-hourly intervals, for patients with severe renal impairment (creatinine clearance less than 10 mL/minute) and to 800 mg three times daily, at intervals of approximately eight hours, for patients with moderate renal impairment (creatinine clearance in the range 10 to 25 mL/minute).

Contraindications
ZOVIRAX tablets and *ZOVIRAX* suspensions are contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

Warnings and Precautions

Use in patients with renal impairment and in elderly patients:
Aciclovir is eliminated by renal clearance; therefore the dose must be reduced in patients with renal impairment (*see Dosage and Administration*). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must 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 be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (*see Adverse Reactions*).

Hydration status: Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.

Interactions
No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. Similarly increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients have been shown when the drugs are coadministered. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Pregnancy and Lactation
Pregnancy
A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of *ZOVIRAX*. The birth defects described amongst *ZOVIRAX* exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause.

The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.

Lactation
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. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg/day. Caution is therefore advised if *ZOVIRAX* is to be administered to a nursing woman.

Effects on Ability to Drive and Use Machines
The clinical status of the patient and the adverse event profile of *ZOVIRAX* should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

Adverse Reactions
The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence 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 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Blood and lymphatic system disorders
Very rare: Anaemia, leukopenia, thrombocytopenia.

Immune system disorders
Rare: Anaphylaxis.

Psychiatric and nervous system disorders
Common: Headache, dizziness.

Very rare: Agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, and coma.

The above events are generally reversible and usually reported in patients with renal impairment, or with other predisposing factors (*see Warnings and Precautions*).

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, abdominal pains.

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes.
Very rare: Hepatitis, jaundice.

Skin and subcutaneous tissue disorders
Common: Pruritus, rashes (including photosensitivity)
Uncommon: Urticaria. Accelerated diffuse hair loss.
Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.
Rare: Angioedema.

Renal and urinary disorders
Rare: Increases in blood urea and creatinine.
Very rare: Acute renal failure, renal pain.
Renal pain may be associated with renal failure.

General disorders and administration site conditions
Common: Fatigue, fever.

3.9. Overdose
Symptoms & signs
Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects.

Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).

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

Treatment
Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may therefore be considered a management option in the event of symptomatic overdose.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
ATC code
Pharmacotherapeutic group: Direct acting antivirals, nucleosides and nucleotides excl. reverse transcriptase inhibitors.

ATC code: J05AB01

Mechanism of action
Aciclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including herpes simplex virus (HSV) types 1 and 2, varicella zoster virus (VZV),

Epstein Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV and CMV.

The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non-infected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

Pharmacodynamic effects
Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment.

Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK however; strains with altered viral TK or DNA polymerase have also been reported. *In vitro* exposure of HSV isolates to aciclovir can also lead to the emergence of less sensitive strains. The relationship between the *in vitro* determined sensitivity of HSV isolates and clinical response to aciclovir therapy is not clear.

All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

Pharmacokinetic Properties
Absorption
Aciclovir is only partially absorbed from the gut. Mean steady state peak plasma concentrations (C_{ssmax}) following doses of 200 mg administered four-hourly were 3.1 micromoles (0.7 micrograms/mL) and equivalent through plasma levels (C_{ssmin}) were 1.8 micromoles (0.4 micrograms/mL). Corresponding C_{ssmax} levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 micromoles (1.2 micrograms/mL) and 8 micromoles (1.8 micrograms/mL) respectively, and equivalent C_{ssmin} levels were 2.7 micromoles (0.6 micrograms/mL) and 4 micromoles (0.9 micrograms/mL).

In adults, mean steady state peak plasma concentrations (C_{ssmax}) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 15 mg/kg were 22.7 micromoles (5.1 micrograms/mL), 43.6 micromoles (9.8 micrograms/mL), 92 micromoles (20.7 micrograms/mL) and 105 micromoles (23.6 micrograms/mL), respectively. The corresponding through levels (C_{ssmin}) 7 h later were 2.2 micromoles (0.5 micrograms/mL), 3.1 micromoles (0.7 micrograms/mL), 10.2 micromoles (2.3 micrograms/mL) and 8.8 micromoles (2.0 micrograms/mL), respectively. In children over 1 year of age similar mean peak (C_{ssmax}) and through (C_{ssmin}) levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg.

Distribution
Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels. Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement is not anticipated.

Elimination
In adults the terminal plasma half-life of aciclovir after administration of intravenous aciclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance indicating that tubular secretion in addition to glomerular filtration contributes to the renal elimination of the drug. 9-carboxymethoxy- methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10 to 15% of the dose excreted in the urine. When aciclovir is given one hour after 1 gram of probenecid the terminal half-life and the area under the plasma concentration time curve is extended by 18% and 40% respectively.

Special patient populations

In patients with chronic renal failure the mean terminal half-life was found to be 19.5 hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

In the elderly total body clearance falls with increasing age, associated with decreases in creatinine clearance, although there is little change in the terminal plasma half-life.

Clinical Studies
There is no information on the effect of *ZOVIRAX* oral formulations on human female fertility. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

Non-Clinical Information
The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir is unlikely to pose a genetic risk to man.

Aciclovir was not carcinogenic in long-term studies in the rat and the mouse.

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 effect of orally administered aciclovir on fertility.

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 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 uncertain.

PHARMACEUTICAL INFORMATION
List of Excipients
As registered locally.

Shelf Life
The expiry date is indicated on the packaging.

Storage
Store below 25°C.
Keep dry.

Nature and Contents of Container
PVC/PVdC/Alumunium/Paper child resistant foil blister.

Incompatibilities
There are no special requirements for use on handling of this product.

Use and Handling
None.

Package Quantities and Registration Number
ZOVIRAX Tablets 200 mg, Box, 5 blisters @ 5 tablets Reg. No. DKI1691601310A1

HARUS DENGAN RESEP DOKTER

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Glaxo Wellcome S.A.
Aranda de Duero, Spain

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