1 VIRUPOS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aciclovir 3.0% w/w

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye ointment

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of herpes simplex keratitis.

4.2 Dose and method of administration

The dosage for all age groups is the same.

A 10 mm ribbon of ointment should be placed inside the lower conjunctival sac five times a day at approximately four hourly intervals.

Treatment should continue for at least 3 days after healing.

4.3 Contraindications

Patients with known hypersensitivity to aciclovir or valaciclovir.

4.4 Special warnings and precautions for use

Patients should be informed that transient mild stinging immediately following application may occur.

Patients should avoid wearing contact lenses when using ViruPOS Ophthalmic Ointment.

Resistant strains have been isolated in vitro and in animals following treatment with aciclovir. HSV strains resistant in vitro to aciclovir have also been isolated from immunecompromised as well as immuno-competent patients receiving aciclovir for Herpes simplex infections. Therefore the potential for the development of resistant HSV strains in patients treated with aciclovir should be borne in mind. The relationship between in vitro sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established.

4.5 Interaction with other medicines and other forms of interaction

No clinically significant interactions have been identified.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy (Category B3)

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of ViruPOS. The registry findings have not shown an increase in the number of birth defects amongst ViruPOS exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.

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

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450 mg/kg/day po), rabbit (50 mg/kg/day, sc and iv) or rat (50 mg/kg/day, sc) when dosed throughout the period of major organogenesis. In additional studies in which rats were given 3 sc doses of 100 mg/kg aciclovir on gestation day 10, fetal abnormalities, such as head and tail anomalies, were reported). The clinical relevance of these findings is uncertain.

There have been no adequate and well controlled studies concerning the safety of aciclovir in pregnant women. Only small amounts are absorbed following application to the eye. It should not be used during pregnancy unless the benefits to the patient clearly outweigh the potential risks to the foetus.

Use in Lactation

Limited human data show that aciclovir does pass into breast milk following systemic administration. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

Effects on 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 effect of orally administered aciclovir on fertility.

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

4.7 Effects on ability to drive and use machines

Eye ointments can affect visual ability and therefore caution is advised when driving or using machines.

4.8 Undesirable effects

Adverse reactions are listed below by MedDRA body system organ class and by frequency.

The frequency categories used are:

Very common $\geq 1/10$,

Common	≥ 1/100 and < 1/10,
Uncommon	≥ 1/1,000 and <1/100,
Rare	≥ 1/10,000 and <1/1,000,
Very rare	<1/10,000.

Clinical trial data have been used to assign frequency categories to adverse reactions observed during clinical trials with aciclovir 3% ophthalmic ointment. Due to the nature of the adverse events observed, it is not possible to determine which events were related to the administration of the drug and which were related to the disease. Spontaneous reporting data has been used as a basis for allocating frequency for those events observed post-marketing.

Immune system disorders:

Very rare: Immediate hypersensitivity reactions including angioedema.

Eye disorders:

Very common: Superficial punctate keratopathy. This did not necessitate an early termination of therapy and healed without apparent sequelae.

Common: Transient mild stinging of the eye occurring immediately following application, conjunctivitis.

Rare: Blepharitis.

Local irritation and inflammation such as blepharitis and conjunctivitis have been reported in patients receiving ViruPOS ophthalmic ointment.

Post-marketing:
There have been very rare reports of immediate hypersensitivity reactions including angiodema with topical aciclovir

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

No untoward effects are likely to occur if the entire contents of a tube containing 135 mg of aciclovir were ingested orally.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Microbiology

Aciclovir is an antiviral agent which is active *in vitro* against *Herpes simplex* virus (HSV) types I and II. However, the relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established. Aciclovir needs to be phosphorylated to the active compound, aciclovir triphosphate, in order to become active against the virus. Such conversion is very limited in normal cells and in addition cellular DNA polymerase is not very sensitive to the active compound. However, in infected cells HSV or VZV-coded thymidine kinase facilitates the conversion of aciclovir to aciclovir monophosphate which is then converted to aciclovir triphosphate by cellular enzymes. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis.

5.2 Pharmacokinetic properties

Aciclovir is absorbed through the corneal epithelium and superficial ocular tissues, and achieves significant concentrations in aqueous humour. Small quantities (2-16% of the applied dose) appear in the urine. In animal studies low levels of aciclovir could be detected in blood after topical application to the eye.

5.3 Preclinical safety data

Mutagenicity:

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir does not pose a genetic risk to man

Carcinogenicity:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White soft paraffin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacture stored at or below 30°C. 4 weeks opened stored at or below 30°C. Discard one month after opening.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

4.5 gm tube.

6.6 Special precautions for disposal

No special precautions.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

AFT Pharmaceuticals Ltd.,
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Auckland
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9 DATE OF FIRST APPROVAL

1/10/2015

10 DATE OF REVISION OF THE TEXT

March 2019

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
March 2019	All	Reformat consistent with new Medsafe Data Sheet Template.