SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT

Brand name: VARIKS

Product name: Aciclovir Cream

Strength: 50mg

Pharmaceutical: Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative Declaration, The active substance should be declared by its recommended INN. Accompanied by itssalt or hydrate form if relevant

Aciclovir

Quantitative Declaration, The quantity of the active substance must be expressed per dosage unit.

Each gram contains Aciclovir 50mg

3. PHARMACEUTICAL FORM

White cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aciclovir Cream is used in preventing or treating infections of the skin caused by the herpes simplex virus or herpes zoster.

4.2 Posology/Dosage and method of administration

FOR EXTERNAL USE ONLY.

Clean and thoroughly dry the area to be treated.

Apply Aciclovir Cream to the affected area every 2 hours, 4-6 times daily for periods of 7 days

4.3 Contraindication

Do not use if allergic to any ingredient in aciclovir cream.

4.4 Special warnings and precautions for use

Only recommended for use on cold sores on the lips and face.

People with particularly severe Herpes labialis should be encouraged to seek medical advice.

Not to be applied to mucous membranes such as inside the mouth or vagina, or on the eye. Particular care should be taken to avoid contact with the eye.

Not for use for the treatment of genital herpes or ocular herpes infections.

Not recommended for use by patients who know they are immunocompromised e.g. by HIV infection, bone marrow transplant or cancer treatment, except on the advice of a doctor.

Cold sore sufferers should be advised to avoid transmitting the virus, particularly when active lesions are present.

The excipient propylene glycol can cause skin irritations and the excipient cetyl alcohol can cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other drug products and other forms of interaction

Probenecid increases the mean half-life and area under the plasma concentration curve of systemically administered Aciclovir. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of Aciclovir. However this is likely to be of little relevance to the cutaneous application of Aciclovir.

No interactions with other drugs have been described for topical Aciclovir.

4.6 Fertility, pregnancy and lactation

Pregnancy

No specific studies of topical Aciclovir have been carried out in pregnant women or nursing mothers.

So far, no relevant plasma levels have been measured and no systemic effects have been observed.

However, use of the cream should be considered only when the potential benefit outweighs the possibility of unknown risks.

In internationally accepted standard tests the systemic administration of Aciclovir did not produce embryotoxic or teratogenic effects in rabbits, rats or mice.

Foetal abnormalities were observed in non-standard tests in rats, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Fertility

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of orally administered Aciclovir on fertility. See Clinical Studies in section 5.2.

There is no experience of the effect of Aciclovir tablets on human female fertility. Aciclovir tablets have been shown to have no definite effect upon sperm count, morphology or motility in man.

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 breast fed infants to Aciclovir doses of up to 0.3 mg/kg/day.

4.7 Effects on ability to drive and use machines

The medicinal product has no influence on the ability to drive or operate machinery.

4.8 Undesirable effects

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.

Skin and subcutaneous tissue disorders

Common

- Mild drying or flaking of the skin

Uncommon

- Itching

Rare

- Erythema

- Contact dermatitis following application. Where sensitivity tests have been conducted, the reactive substances have most often been shown to be components of the cream base rather than Aciclovir.

Immune system disorders

Very rare

- Immediate hypersensitivity reactions including angioedema.

After application of the cream, transient burning or stinging of the treated skin areas may occur.

4.9 Overdose

Overdose is unlikely to occur, if the cream is applied locally as indicated. There are no reports concerning an overdose of Aciclovir cream.

No unwanted effects would be expected if the entire contents of a 2.0 g tube of the cream were ingested. Doses of 800 mg five times daily (4 g per day), have been administered without adverse effects. Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects. Aciclovir is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Aciclovir is a pharmacologically inactive substance. After penetration into cells which are infected with herpes simplex virus types I and II (HSV I & HSV II) or varicella-zoster virus (VSV), Aciclovir is converted into a virostatic agent. The conversion of Aciclovir is catalysed by viral HSV- or VZV- thymidine kinase. Human thymidine kinase does not use Aciclovir effectively as a substrate; hence the toxicity to mammalian host cells is low.

In the infected cell, Aciclovir is phosphorylated by viral thymidine kinase to Aciclovir monophosphate, which is further converted by cellular enzymes to Aciclovir triphosphate. Aciclovir triphosphate has a greater affinity for viral DNA polymerase than host cell DNA polymerase and therefore selectively interferes with the viral enzyme causing inhibition of viral DNA replication. Aciclovir is also incorporated into viral DNA by viral DNA polymerase, which results in chain termination, as Aciclovir lacks a 3'-hydroxyl group, preventing addition of nucleotides by 3', 5'-linkage.

In several immunocompromised patients a longer or repeated treatment with Aciclovir can lead to a selection of viral strains with reduced sensitivity. As a result, these patients no longer respond to treatment with Aciclovir. Most of the clinical isolates with reduced sensitivity showed a relative lack of virus thymidine kinase. However, strains with changed/different virus thymidine kinase or DNA polymerase were also reported. The in vitro exposition of HSV-isolates can also lead to the development of less sensitive strains. The connection between the in vitro determined sensitivity of HSV-isolates and the clinical response to the treatment with Aciclovir is not clear.

In two large, double blind, randomised clinical studies involving 1,385 subjects treated over 4 days for recurrent herpes labialis, Aciclovir Cream 5% was compared to vehicle cream. In these studies, time from start of treatment to healing was 4.6 days using Aciclovir Cream and 5.0 days using vehicle cream ($p<0.001$). Duration of pain was 3.0 days after start of treatment in the Aciclovir Cream group and 3.4 days in the vehicle group ($p=0.002$). Overall, approximately 60% of patients started treatment at an early lesion stage (prodrome or erythema) and 40% at a late stage (papule or blister). The results were similar in both groups of patients.

5.2 Pharmacokinetic properties

Absorption and plasma concentrations

Aciclovir penetrates into the skin. The intracutaneous concentration levels are higher than the minimal inhibitory concentration (MIC) in tissue at steady state.

After topical application of Aciclovir, no Aciclovir plasma concentration could be determined.

As the Aciclovir plasma concentrations following topical application are below the limit of detection, no pharmacokinetic studies are available on topical Aciclovir. Therefore, the following data is based on the data after oral or intravenous administration.

Plasma protein binding is reported to range between 9% and 33% as a function of dose. The volume of distribution at steady state in adults is 50 ± 8.71v1.73 m2, or 0.7 l/kg.

Two metabolites could be identified in the urine of patients with normal renal function after single dosing with 14C-Aciclovir: 9-carboxymethoxymethylguanine (2%-14% of an administered dose) and 8-hydroxy-9-(2-hydroxyethoxymethyl) guanine (<0.2% of a dose). Subjects with normal renal function eliminate 62%-91% of an Aciclovir dose unchanged and 9%-14% as 9-carboxymethoxymethylguanine via the kidneys.

Aciclovir is predominantly eliminated via the kidneys, preliminary by glomerular filtration and to a lesser extent by tubular secretion.

In vitro and in vivo studies of Aciclovir cream and Aciclovir ointment versus oral Aciclovir were carried out to determine the bioavailability of Aciclovir in human skin. The in vitro studies used human skin biopsies, whilst the bioassays either used human skin grafts on mice or were carried out in the human eye (3 patients).

The following dermal drug concentration gradient emerged for both topical and oral Aciclovir: stratum corneum> epidermis> dermis. There was no difference in concentration between cream and ointment.

The upper layer of the epidermis on average showed a 48-fold higher concentration following topical application of Aciclovir ointment or cream 5% than after oral dosing, but the drug concentration in the basal epidermis – the site of herpes virus infection – was 2 to 3 times lower following topical application than after oral dosing.

On the basis of continuous absorption the concentration increased as a function of time (higher drug concentrations being found 48 hours post-topical dose than 24 hours post-topical dose).

Thus short dosing intervals appear rational for the special treatment of herpes simplex virus (HSV) infections.

Clinical Studies

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.

5.3 Preclinical safety data

For 24 days, PEG-based Aciclovir Cream 5% or 10% was applied to the shaved (intact and grazed) skin of guinea-pigs. The treated area corresponded to 10% of the body surface. There were neither systemic nor local toxic symptoms. This is also confirmed by histological studies and autopsy. According to the test carried out by Draize, who evaluated the allergic sensitising potential of a substance, there were no pathogenic findings.

Studies carried out in swine showed that 5% Aciclovir cream in a PEG vehicle caused an only minimal (quantitative) delay in epidermal wound healing.

Rabbits had 1%, 3% or 6% Aciclovir cream in a white petrolatum vehicle introduced directly into both eyes 5 times daily at 90-minute intervals for 3 weeks. Neither autopsy nor inspection nor histological examination revealed any pathological changes in the rabbit eyes.

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.

Aciclovir was not found to be 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 at systemic 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White soft paraffin ,Glyceryl Monostearate, Cetostearyl Alcohol, Liquid Paraffin, Paregal O , Glycerin , Ethylparaben , Ethanol, Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in dry place away from sunlight.

Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

Collapsible aluminum tube having a screw threaded neck finish sealed with an aluminum membrane. Each tube is supplied with a white polyethylene screw cap which has a piercing tip to puncture open the aluminum membrane on the neck.

Pack size:5g, 10g

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7. APPLICANT/HOLDER OF CERTIFICATE F PRODUCT REGISTRATION

Applicant: AKSO PHARMACEUTICAL NIGERIA LIMITED..

Adress: No. 320, Odusami Street, off Wempco Road, Ogba , Lagos Nigeria

E-mail: 506798052@qq.com

Contact person : Brian Fu

Tel: 09118269061

8. DRUG PRODUCT MANUFACTURER

Manufacturer name: FRONT PHARMACEUTICAL PLC

Physical address: No.369 Baocheng Road, Xuancheng Economic and Technical Development Zone, Anhui, China

Tel: 86-0563-2625199

Fax: 86-0563-2625199

E-mail: export@frontpharm.com

9. NAFDAC REGISTRATION NUMBER(S)