PACKAGE INSERT FOR

CIPLAFAM 125 / 250 TABLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAMES (AND DOSAGE FORM):

CIPLAFAM 125 (Tablet)

CIPLAFAM 250 (Tablet)

COMPOSITION:

CIPLAFAM 125: Each film-coated tablet contains famciclovir 125 mg.

CIPLAFAM 250: Each film-coated tablet contains famciclovir 250 mg.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8. Antiviral agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Famciclovir is converted *in vivo* into penciclovir, which has demonstrable *in vivo* and *in vitro* activity against Herpes simplex viruses (types 1 and 2), Varicella-Zoster virus, Epstein-Barr virus and cytomegalovirus. Famciclovir is the oral form of penciclovir. The antiviral effect of orally administered famciclovir has been demonstrated in several animal models. This effect is due to *in vivo* conversion to penciclovir. Penciclovir targets virus-infected cells where it is converted into the triphosphate (mediated via

virus-induced thymidine kinase). Penciclovir triphosphate persists in infected cells for more than 12 hours where it inhibits replication of viral DNA. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable. Accordingly, uninfected cells are unlikely to be affected by therapeutic concentrations of penciclovir. Penciclovir has been shown to be active against a recently isolated acyclovir-resistant Herpes simplex virus strain which has an altered DNA polymerase.

Pharmacokinetic properties:

After oral administration, famciclovir is absorbed and converted to the antiviral active compound, penciclovir. Bioavailability of penciclovir following oral administration of famciclovir is 77 %. Mean peak plasma concentration of penciclovir, following a 125 mg and 250 mg oral dose of famciclovir, was 0,8 microgram/ml and 1,6 microgram/ml, respectively, and occurred at a median time of 45 minutes post-dose. Plasma concentration-time curves of penciclovir are similar following single and repeat (three and two times daily) dosing. The terminal plasma half-life of penciclovir after both single and repeat dosing with famciclovir, is approximately 2,0 hours. There is no accumulation of penciclovir on repeated dosing with famciclovir.

Penciclovir and its 6-deoxy precursor are poorly (< 20 %) bound to plasma proteins. Famciclovir is eliminated, principally as penciclovir and its 6-deoxy precursor which are excreted in urine unchanged. Famciclovir has been undetected in urine. Tubular secretion, contributes to the renal elimination of the compound. Uncomplicated herpes zoster infection does not significantly alter the pharmacokinetics of penciclovir measured following oral administration of famciclovir.

INDICATIONS:

CIPLAFAM is indicated in the following:

- For the treatment of herpes zoster (shingles) infection.
- For the treatment of first episode herpes genitalis within 72 hours of appearance of symptoms and recurrent genital herpes infections within 6 hours of appearance of symptoms.
- For the suppression of recurrent genital herpes in immunocompetent patients.

CONTRA-INDICATIONS:

CIPLAFAM is contra-indicated in the following:

- Known hypersensitivity to famciclovir, penciclovir or any of the constituents of **CIPLAFAM**.
- Pregnant and lactating women (see **"PREGNANCY AND LACTATION"**).

WARNINGS:

None reported.

INTERACTIONS:

No clinically significant interactions have been reported with the use of **CIPLAFAM**. Evidence from preclinical studies has shown no potential for induction of cytochrome P450. Probenecid and other medicines that affect renal physiology may affect plasma levels of penciclovir.

PREGNANCY AND LACTATION:

The use of **CIPLAFAM** during pregnancy and lactation is not recommended as safety

and efficacy have not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults:

***Herpes zoster* (shingles) infections:**

250 mg three times daily for seven days. Treatment should be initiated within 72 hours after rash onset.

First episode genital herpes infections:

Within 72 hours of appearance of symptoms 250 mg three times daily for five days.

Recurrent genital herpes infections:

Within 6 hours of appearance of symptoms 125 mg twice a day for five days.

Suppression of recurrent genital herpes infections in immunocompetent patients:

125 to 250 mg twice daily.

The length of treatment depends upon the severity of the disease. Therapy should be re-evaluated after 12 months in order to observe possible changes in the natural history of the disease.

Dosage in elderly:

Dosage modification is not required unless renal function is impaired.

Dosage in children:

There are currently insufficient data on the safety and efficacy of **CIPLAFAM** in children, and therefore its use in children is not recommended.

Dosage in renally impaired patients:

Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to dosages in patients with impaired renal function. The following modifications in dosage are recommended:

For the treatment of herpes zoster infections:

Creatinine Clearance (ml/min/1,73 m^2)	***Dosage***
> 40	250 mg 8 hourly
30 to 39	250 mg 8 or 12 hourly
10 to 29	125 mg 8 or 12 hourly

For the treatment of first episode genital herpes infections:

Creatinine Clearance (ml/min/1,73 m^2)	***Dosage***
> 30	250 mg 8 hourly
10 to 29	125 mg 8 hourly

For the treatment of recurrent genital herpes infections:

Creatinine Clearance (ml/min/1,73 m^2)	***Dosage***
> 10	125 mg 12 hourly

For the suppression of recurrent genital herpes infections in immunocompetent

patients:

Creatinine Clearance (ml/min/1,73 m^2)	***Dosage***
> 30	250 mg 12 hourly
10 to 29	125 mg 12 hourly

When only serum creatinine is available, a nomogram or the following formula (modified Cockcroft and Gault) should be used to estimate creatinine clearance in adults.

$$\text{eGFR (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (µmol/L)}}$$

For females multiply the GFR by 0,85.

Renally impaired patients on haemodialysis:

Since 4 hours haemodialysis results in approximately 75 % reduction in plasma concentrations of penciclovir, famciclovir should be administered immediately following dialysis. The recommended dose is 250 mg (herpes zoster patients) and 125 mg (genital herpes patients).

Dosage in hepatically impaired patients:

No dosage modification is required for patients with well-compensated chronic liver disease. There is no information on patients with overtly decompensated chronic liver disease, accordingly no precise dose recommendations can be made for this group of patients.

Maximum tolerated daily dose and duration:

Herpes zoster patients receiving 750 mg three times daily for seven days tolerated the **CIPLAFAM** therapy well. Genital herpes patients receiving up to 750 mg three times daily for 5 days and up to 500 mg three times daily for 10 days also tolerated the product well. Good tolerance was also seen in two 12 months studies, in which genital herpes patients received doses of up to 250 mg three times daily.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Use of **CIPLAFAM** may result in the following side-effects:

Nervous system and psychiatric disorders:

Frequent: Headache, confusion.

Less frequent: Dizziness, somnolence.

Gastro-intestinal system disorders:

Less frequent: Nausea, diarrhoea, and vomiting.

Hepatobiliary disorders:

Less frequent: Jaundice.

Skin and subcutaneous tissue disorders:

Less frequent: Rash, pruritus, urticaria.

Special attention should be paid to patients with impaired renal function and dosage adjustment is necessary (see **"DOSAGE AND DIRECTIONS FOR USE"** and

"KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT"). No special precautions are required for patients with well-compensated liver disease or elderly patients with normal renal function. Genital herpes is a sexually transmitted disease. The risk of transmission is increased during acute episodes. Patients should be advised to avoid intercourse when symptoms are present even if treatment with an antiviral has been initiated.

During suppressive treatment with antiviral agents, the frequency of viral shedding is significantly reduced. However, the risk of transmission is still theoretically possible. Patients should therefore take appropriate steps for protected intercourse.

Effects on the ability to drive or use machines:

There is no evidence that **CIPLAFAM** will affect the ability of a patient to drive or to use machines. However, patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking **CIPLAFAM** should refrain from driving or operating machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No acute overdosage with **CIPLAFAM** has been reported. Symptomatic and supportive therapy should be given as appropriate. Acute renal failure has been reported in patients with underlying renal disease where the famciclovir dosage has not been appropriately reduced for the level of renal function. Penciclovir is dialysable, and plasma concentrations are reduced by approximately 75 % following 4 hours haemodialysis.

IDENTIFICATION:

CIPLAFAM 125: White to off-white coloured, circular, biconvex, film-coated tablets plain on both sides.

CIPLAFAM 250: White to off-white coloured, circular, biconvex, film-coated tablets plain on both sides.

PRESENTATION:

CIPLAFAM 125: Supplied in white, opaque PVC/PVDC and aluminium foil blister strips packed as 10 tablets.

CIPLAFAM 250: Supplied in white, opaque PVC/PVDC and aluminium foil blister strips packed as 15, 21, 56 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C, in a dry place.

KEEP OUT OF THE REACH OF CHILDREN.

Keep the blisters in the outer carton until required for use.

REGISTRATION NUMBERS:

CIPLAFAM 125: 42/20.2.8/0667

CIPLAFAM 250: 42/20.2.8/0668

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

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