PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MACLEODS FAMCICLOVIR TABLETS 125 mg (film-coated tablet)

MACLEODS FAMCICLOVIR TABLETS 250 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MACLEODS FAMCICLOVIR TABLETS 125 mg: Each film-coated tablet contains 125 mg famciclovir. Contains sugar (2,550 mg lactose anhydrous).

MACLEODS FAMCICLOVIR TABLETS 250 mg: Each film-coated tablet contains 250 mg famciclovir. Contains sugar (5,100 mg lactose anhydrous).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MACLEODS FAMCICLOVIR TABLETS 125 mg : A white to off white, round shaped, biconvex, film coated tablet engraved with “ML 67” on one side and plain on the other side.

MACLEODS FAMCICLOVIR TABLETS 250 mg : A white to off white, round shaped, biconvex, film coated tablet engraved with “ML 70” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MACLEODS FAMCICLOVIR TABLETS is indicated for the treatment of herpes zoster (shingles) infection.

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MACLEODS FAMCICLOVIR TABLETS is indicated 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.

MACLEODS FAMCICLOVIR TABLETS is indicated for the suppression of recurrent genital herpes in immunocompetent patients.

4.2 Posology and method of administration

Posology

Dosage in 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 infection:

Within 72 hours of appearance of symptoms 250 mg three times daily for 5 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 on 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 **MACLEODS FAMCICLOVIR TABLETS** in children, and therefore its use in children is not recommended.

Dosage in renal impairment:

Because reduced clearance of penciclovir is related to reduced renal function, as measured by creatinine clearance, special attention should be given to patients with impaired renal function.

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The dose of **MACLEODS FAMCICLOVIR TABLETS** should be modified as follows in patients with significantly impaired renal function:

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 creatine is available, a nomogram or the following formula (Cockcroft and Gault) should be used to estimate creatine clearance:

Formula to estimate creatine clearance (ml/min/1,73 m^2):

$$\left(\frac{[140 - \text{age in years}] \times \text{weight (kg)}}{(72 \times \text{serum creatinine } \mu\text{mol/l})} \right)$$

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x **either** 88,5 (for males) **or** 75,2 (for females)

Renally impaired patients on haemodialysis:

Since 4 hours haemodialysis results in approximately 75 % reduction in plasma concentrations of penciclovir, **MACLEODS FAMCICLOVIR TABLETS** should be administered immediately following haemodialysis. 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 **MACLEODS FAMCICLOVIR TABLETS** 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 seen in two 12 month studies, in which genital herpes patients received doses of up to 250 mg three times daily.

Method of administration

Oral use

4.3 Contraindications

- Hypersensitivity to famciclovir, penciclovir or any of the components of **MACLEODS FAMCICLOVIR TABLETS** excipients listed in section 6.1.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and special precautions for use

Renal impairment:

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Special attention should be paid to patients with impaired renal function and dosage adjustments is necessary (see sections 4.2 and 4.9).

No special precautions are required for elderly patients with normal renal function.

Hepatic impairment:

No special precautions are required for patients with well compensated liver disease.

MACLEODS FAMCICLOVIR TABLETS has not been studied in patients with severe hepatic impairment. Conversion of famciclovir to its active metabolite penciclovir may be impaired in these patients resulting in lower penciclovir plasma concentrations, and thus a decrease of efficacy of **MACLEODS FAMCICLOVIR TABLETS** may occur.

Use for herpes zoster treatment:

Patients with complicated herpes zoster, i.e. those with visceral involvement, disseminated zoster, motor neuropathies, encephalitis and cerebrovascular complications should be treated with intravenous antiviral therapy.

Immunocompromised patients with ophthalmic zoster or those with a high risk for disease dissemination and visceral organ involvement should be treated with intravenous antiviral therapy.

Transmission of genital herpes:

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, transmission is still possible. Therefore, it is recommended that patients take appropriate steps for protected intercourse.

Lactose intolerance:

MACLEODS FAMCICLOVIR TABLETS contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **MACLEODS FAMCICLOVIR TABLETS**.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

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4.5 Interactions with other medicines and other forms of interaction

No clinically significant interactions have been identified.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450. Probenecid and other medicines that affect renal physiology could affect plasma levels of penciclovir. In a phase I study no medicine interactions were observed after co-administration with zidovudine and famciclovir.

Famciclovir needs aldehyde oxidase to be converted into penciclovir, its active metabolite. Raloxifen has been shown to be a potent inhibitor of this enzyme *in vitro*. Co-administration of raloxifen could affect the formation of penciclovir and thus the efficacy of **MACLEODS FAMCICLOVIR TABLETS**. When raloxifen is co-administered with **MACLEODS FAMCICLOVIR TABLETS** the clinical efficacy of the antiviral therapy should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **MACLEODS FAMCICLOVIR TABLETS** is contra-indicated during pregnancy (see section 4.3).

Breastfeeding

The use of **MACLEODS FAMCICLOVIR TABLETS** is contra-indicated during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

MACLEODS FAMCICLOVIR TABLETS may cause dizziness, somnolence, confusion and hallucinations which could adversely affect the ability of patients to drive and use machinery.

4.8 Undesirable effects

MACLEODS FAMCICLOVIR TABLETS has not been studied in ophthalmic zoster, disseminated zoster or in immunocompromised patients.

Headache and nausea have been reported in clinical trials. VR

The following side effects have been reported

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	**Less frequent**	Thrombocytopenia
Immune system disorders	**Less frequent**	Angiodema
Psychiatric disorders	**Less frequent**	Confusion (predominantly in the elderly), hallucinations
Nervous system disorders	**Frequent**	Headache, dizziness
	Less frequent	Somnolence (predominantly in the elderly)
Cardiac disorders	**Less frequent**	Palpitations
Gastrointestinal disorders	**Frequent**	nausea, vomiting, abdominal pain, diarrhoea
Hepatobiliary disorders	**Frequent**	Abnormal liver function tests
	Less frequent	Cholestatic jaundice
Skin and subcutaneous tissue disorders	**Frequent**	Rash, pruritis
	Less frequent	Urticaria
	Frequency not known	Serious skin reactions (e.g. erythema multiforme, Stevens-Johnson Syndrome, Toxic

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		Epidermal Necrolysis), leukocytoclastic vasculitis.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptomatic and supportive therapy should be given as appropriate. Acute renal failure has been reported in patients where the famciclovir dosage has not been appropriately reduced for the level of renal function. Penciclovir is dialysable and plasma concentrations are reduced by ~75 % following 4 hours haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Other hypotensives

Pharmacodynamic properties

Famciclovir is the oral form of penciclovir. Famciclovir is the diacetyl ester prodrug of 6-deoxy penciclovir and lacks intrinsic antiviral activity. Penciclovir is an acyclic guanine nucleoside analogue. Famciclovir is converted *in vivo* into penciclovir, which has demonstrated *in vivo* and *in vitro* activity against herpes simplex viruses (types 1 and 2), varicella zoster virus, Epstein-Barr virus and cytomegalovirus. 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 120 hours where it inhibits replication of viral DNA.

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Penciclovir has been shown to be active against a recently isolated acyclovir-resistant Herpes simplex virus strain which has an altered DNA polymerase.

5.2 Pharmacokinetic properties

Absorption:

Oral penciclovir has low (< 5 %) bioavailability. In contrast, famciclovir is well absorbed orally (bioavailability ~ 75 %) and is converted rapidly by deacetylation of the side chain and oxidation of the purine ring during and following absorption from the intestine. Thus, the bioavailability of penciclovir is ~ 75 % following oral administration of famciclovir.

Food slows absorption but does not reduce overall bioavailability.

Metabolism:

The mean peak penciclovir concentrations are 0,8 µg/ml and 1,6 µg/ml following a 125 mg and 250 mg oral dose of famciclovir respectively, and occur at a median time of 45 minutes post-dose.

The penciclovir pharmacokinetics profiles are similar after single and repeat (twice a day and three times a day) dosing. There is no accumulation of penciclovir on repeated dosing with famciclovir. Binding of penciclovir and its 6-deoxy precursor to plasma protein is very low (< 20 %).

The terminal plasma half-life of penciclovir after both single and multiple dosing with famciclovir is approximately 2,0 hours.

A small quantity of the 6-deoxy precursor but no famciclovir is detectable in plasma. After intravenous infusion of penciclovir at 10 mg/kg, peak plasma levels average 12 µg/ml. The volume of distribution is about twice the volume of total-body water.

Elimination

The plasma elimination $t_{1/2}$ of penciclovir averages ~2 hours, and > 90 % is excreted unchanged in the urine, probably by both filtration and active tubular secretion. Following oral famciclovir administration, nonrenal clearance accounts for ~10 % of each dose, primarily through faecal excretion, but penciclovir (60 % of dose) and 6-deoxy precursor (< 10 % of dose) are eliminated primarily in the urine.

Special populations

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The plasma $t_{1/2}$ averages 9,9 hours in renal insufficiency (Cl_{cr} < 30 ml/minute); hemodialysis efficiently removes penciclovir.

Lower peak plasma concentrations of penciclovir, but no reduction in overall bioavailability of famciclovir occur in compensated chronic hepatic insufficiency.

Uncomplicated herpes zoster infection does not significantly alter the pharmacokinetics of penciclovir measured after the oral administration of famciclovir.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose anhydrous

Low substituted hydroxypropyl cellulose

Sodium starch glycollate

Hydroxypropyl cellulose

Magnesium stearate

Hypromellose 5 cps

Titanium dioxide

Polyethylene glycol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C in a cool and dry place. The bottles must be kept tightly closed.

6.5 Nature and contents of container

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MACLEODS FAMCICLOVIR TABLETS 125 mg and 250 mg:

30's HDPE bottle pack with child resistant closure:

High density polyethylene (HDPE) bottle pack comprises of white opaque HDPE bottle provided along with a white, polypropylene (PP) screw cap with pulp and heat seal liner packed in an outer carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBER:

MACLEODS FAMCICLOVIR TABLETS 125 mg: 45/20.2.8/1157

MACLEODS FAMCICLOVIR TABLETS 250 mg: 45/20.2.8/1158

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 20 March 2018

10. DATE OF REVISION OF THE TEXT

26 June 2023

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