Rivofam®

Famciclovir

FORMS AND PRESENTATION

Rivofam® 125: Film coated tablets: Box of 15.
Rivofam® 250: Film coated tablets: Box of 15.
Rivofam® 500: Film coated tablets: Box of 10 or 20.
Rivofam® 750: Film coated tablets: Box of 10.

COMPOSITION

Rivofam® 125: Each film coated tablet contains Famciclovir 125mg.
Rivofam® 250: Each film coated tablet contains Famciclovir 250mg.
Rivofam® 500: Each film coated tablet contains Famciclovir 500mg.
Rivofam® 750: Each film coated tablet contains Famciclovir 750mg.
Excipients: hydroxypropyl cellulose, lactose, sodium starch glycolate, hydroxypropyl methylcellulose, magnesium stearate, polysorbate, polyethylene glycol, titanium dioxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antivirals for systemic use.
ATC code: J05AB09.

Famciclovir is a prodrug. After absorption, Famciclovir is rapidly converted to penciclovir, which has demonstrable *in vitro* activity against *herpes simplex* (HSV) (types 1 and 2) and *varicella zoster* (VZV) and *Epstein-Barr* (EBV) viruses. The drug exhibits only limited activity *in vitro* against *cytomegalovirus.*

The antiviral effect of orally administered Famciclovir has been demonstrated in several animal models, including various studies in HSV-infected mice. This effect is due to *in vivo* conversion to penciclovir. Penciclovir targets virus-infected cells, where it is rapidly and efficiently converted into the triphosphate by viral thymidine kinase (TK).

Penciclovir triphosphate persists in infected cells for more than 12 hours where it inhibits replication of viral DNA and has a half-life of 9, 10 and 20 hours in cells infected with v*aricella zoster, herpes simplex* virus type 1 and *herpes simplex* virus type 2 respectively. 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.

The most common form of resistance encountered with aciclovir among HSV strains is a deficiency in the production of the TK enzyme. Such TK-deficient strains would be expected to be cross-resistant to both penciclovir and aciclovir.

Pharmacokinetic properties

Absorption

Following oral administration, Famciclovir is rapidly absorbed and extensively converted to penciclovir. The bioavailability of penciclovir after oral administration of Famciclovir is 77%.

Distribution and Biotransformation

Mean peak plasma concentrations of penciclovir, following 125 mg, 250 mg and 500 mg oral doses of Famciclovir, were 0.8 micrograms/ml, 1.6 micrograms/ml and 3.3 micrograms/ml, respectively, and occurred at a mean time of 45 minutes post-dose. Slight passage of the metabolites across the blood-brain barrier was observed in rats. Penciclovir clearance is reduced in patients with renal impairment. The bioavailability of penciclovir is unaffected by hepatic impairment, but the mean peak plasma level is diminished. Ingestion with food leads to lower mean peak penciclovir concentrations, without effect on its bioavailability.

Plasma concentration-time curves of penciclovir are similar following single and repeat (two or three times daily) dosing. The terminal plasma half-life of penciclovir after both single and repeat dosing with Famciclovir is approximately 2 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.

Elimination

Famciclovir is eliminated principally as penciclovir and its 6-deoxy precursor which are excreted in urine. No unchanged Famciclovir can be detected in urine. Tubular secretion contributes to the renal elimination.

INDICATIONS

Rivofam® is indicated in:

- Treatment of genital herpes infections (initial and recurrent epidoses) in immunocompetent patients.
- Suppression of recurrent genital herpes infections in immunocompetent patients.
- Treatment of herpes zoster infections of the skin and mucous membranes in immunocompetent patients in whom a severe course of infection is anticipated, including herpes zoster ophthalmicus.
- Treatment of herpes zoster and herpes simplex infections in immune-compromised patients.

CONTRAINDICATIONS

- Hypersensitivity to Famciclovir, penciclovir or to any of the excipients.

PRECAUTIONS

- Special attention should be paid to patients with impaired renal function as dosage adjustment may be necessary. No special precautions are required for hepatically impaired or elderly patients with normal renal function.
- Genital herpes is a sexually transmitted disease. Patients should avoid sexual intercourse when symptoms are present even if treatment with an antiviral has been initiated, in order to protect their partners.
- During 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 (i.e. use condoms).

Ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness, somnolence, confusion or other central nervous system disturbances while taking Famciclovir should refrain from driving or operating machinery.

PREGNANCY AND LACTATION

There is no adequate data from the use of Famciclovir/penciclovir in pregnant women. Studies in animals have not shown reproductive toxicity. The potential risk for humans is unknown. Famciclovir should not be used during pregnancy unless the potential benefits of treatment for the mother outweigh any possible risk for the child.

It is unknown whether Famciclovir/penciclovir is excreted in human breast milk. Animal studies have shown excretion of Famciclovir/penciclovir in breast milk. Famciclovir should not be used during breast-feeding.

DRUG INTERACTIONS

No clinically significant interactions have been identified. Probenecid and other substances that affect renal physiology could affect the plasma levels of penciclovir. Account must be taken of the possibility of interactions with substances eliminated by active tubular excretion such as acetylsalicylic acid, ibuprofen.

Evidence from preclinical studies has shown no potential for induction of cytochrome P450. In a Phase I study, no interactions were observed after co-administration of zidovudine and Famciclovir.

ADVERSE EFFECTS

The adverse reactions reported are classified by system organ class and ordered by frequency. Frequencies are defined as: Common (≥ 1/100 to < 1/10), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000); Not known (cannot be estimated from the available data).

- Blood and lymphatic system disorders: Thrombocytopenia (very rare).
- Nervous system disorders: Headache (common); dizziness, fatigue, somnolence (predominantly in the elderly) (very rare).
- Gastrointestinal disorders: Nausea, diarrhea, vomiting, abdominal pain, constipation (common).
- Skin and subcutaneous tissue disorders: Increased tendency to sweat, pruritus (common); serious skin reactions, e.g. erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis; rash, urticaria (very rare).
- General disorders and administration site conditions: Fever (not known).

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- Hepatobiliary disorders: Jaundice, abnormal liver function tests (very rare).
- Psychiatric disorders: Confusion (predominantly in the elderly) (rare); hallucinations (very rare).

DOSAGE AND ADMINISTRATION

Adults

- First-episode genital herpes infections:

250 mg three times daily for 5 days.

The first dose should be taken as soon as possible after the onset of the infection.

- Recurrent genital herpes infections:

250 mg twice daily for 5 days.

Initiation of treatment is recommended during the prodromal period or as soon as possible after the onset of lesions.

- Suppression of genital herpes infections in immunocompetent patients:

250 mg twice daily. The duration of treatment depends on the severity of the disease.

Therapy should be interrupted periodically at intervals of 6 to 12 months in order to observe possible changes in the natural history of the disease. The long-term use of Rivofam® is not recommended.

A dose of 500 mg twice daily has been shown to be effective in HIV patients.

- Herpes zoster infections, including herpes zoster ophthalmicus in immunocompetent patients:

500 mg three times daily for 7 days or 750 mg twice daily* for 7 days.

Initiation of treatment is generally recommended as soon as possible (within 48 hours) of the onset of rash.

- Herpes zoster infections in immune-compromised patients:

500 mg three times daily for 10 days.

Initiation of treatment is generally recommended as soon as possible (within 48 hours) of the onset of rash.

- Herpes simplex infections in immune-compromised patients:

500 mg twice daily for 7 days.

Initiation of treatment is recommended as soon as possible after the onset of lesions.

Elderly

Dosage modification is not required, unless renal function is impaired.

Children

Rivofam® is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy.

Renally impaired patients

Special attention should be given to dosage in patients with impaired renal function, as reduced clearance of penciclovir is related to impaired renal function measured in relation to creatinine clearance. The following dosage is recommended in renally impaired patients:

Immunocompetent patients

- For the treatment of herpes zoster or first-episode genital herpes infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30 - 59	250 mg once daily
10 - 29	125 mg once daily

- For the treatment of acute recurrent genital herpes infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30 - 59	250 mg once daily
10 - 29	125 mg once daily

- For the suppression of recurrent genital herpes infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
≥ 30	No Adjustment
10 - 29	125 mg once daily

Immuno-compromised patients

- For the treatment of herpes zoster infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30 - 59	250 mg twice daily
10 - 29	125 mg once daily

- For the treatment of herpes simplex infections:

Creatinine clearance (ml/min/1.73m^2)	Dosage
30 - 59	250 mg twice daily
10 - 29	125 mg once daily

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

Formula to estimate creatinine clearance (ml/min/1.73 m^2):

[140 - age in years] x weight (kg) x *either* 88.5 (for males) or 75.2 (for females)

72 x serum creatinine (µmol/l)

Renally impaired patients on hemodialysis

A dose interval of 48 hours is recommended for hemodialysis patients for periods between dialysis. Famciclovir must be administered immediately after dialysis, as 4 hours of hemodialysis reduce the plasma penciclovir concentration by approximately 75%.

The recommended dose is one standard dose for first episode or recurrent genital herpes infections and for herpes zoster patients.

Hepatically impaired patients

Dosage modification is not required for patients with well compensated chronic liver disease. No data are available on patients with decompensated chronic liver disease; accordingly no precise dose recommendations can be made for this group of patients.

Method of administration

For oral administration.

Famciclovir can be administered with or without food.

Parenteral treatment is recommended for severely ill patients.

* Only relevant for the 750 mg strength.

OVERDOSAGE

Overdose experience with Famciclovir is limited. A report of accidental acute overdosage (10.5 g) was asymptomatic. In a report of chronic use (10 g/day for two years), Famciclovir was well tolerated. In the event of an overdose supportive and symptomatic therapy should be given as appropriate.

Acute renal failure has been reported rarely 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 of hemodialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: November 2014.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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