Valcyk®Benta

Valaciclovir Hydrochloride

FORMS AND PRESENTATION

Valcyk®Benta: Film-coated tablets: Box of 50.

COMPOSITION

Valcyk®Benta: Each film coated tablet contains: Valaciclovir hydrochloride equivalent to Valaciclovir 500 mg. Excipients: microcrystalline cellulose, crospovidone, povidone, magnesium stearate, opadry white.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Valaciclovir, an antiviral, is the L-valine ester of aciclovir. Aciclovir is a purine (guanine) nucleoside analogue.

Mode of Action: Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as Valaciclovir hydrolase. Aciclovir is a specific inhibitor of the herpes viruses with in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of UL97. This requirement for activation of aciclovir by a virus specific enzyme largely explains its selectivity. The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacokinetic Properties

After oral administration, Valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by an enzyme isolated from human liver referred to as Valaciclovir hydrolase. The bioavailability of aciclovir from 1000 mg Valaciclovir is 54%, and is not reduced by food. Mean peak aciclovir concentrations are 2.2-8.3 µg/ml following single doses of 250-2000 mg Valaciclovir to healthy subjects with normal renal function, and occur at a median time of 1-2 hrs post dose. Peak plasma concentrations of Valaciclovir are 4% of aciclovir levels, occur at a median time of 30-100 minutes post dose. The Valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing. The binding of Valaciclovir to plasma proteins is 15%. The elimination plasma half-life of aciclovir after both single and multiple dosing with Valaciclovir is 3 hrs. In patients with end-stage renal disease, the elimination half-life of aciclovir after Valaciclovir administration is about 14 hrs. Less than 1% of the administered dose of Valaciclovir is recovered in the urine unchanged. Valaciclovir is eliminated principally as aciclovir (more than 80% of the recovered dose) and CMMG, 9-(carboxymethoxy) methylguanine, the known aciclovir metabolite.

For Prevention and Treatment

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Helps to:

- **Treat herpes zoster and herpes simplex infections**
- **Avoid recurrent herpes simplex infections**
- **Reduce genital herpes transmission risk**
- **Prevent CMV disease after renal transplantation**

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Before prescribing please consult physicians' circular.

® Registered trade name

Valcyk® Benta manufactured by BPI

CE GMP

Benta Pharma Industries - Dbayeh, Lebanon

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INDICATIONS

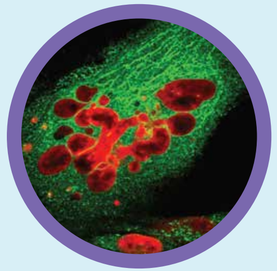
Valcyk®Benta is indicated for the treatment of herpes zoster (shingles).
Valcyk®Benta is indicated for the treatment of herpes simplex infections of the skin and mucous membranes, including initial and recurrent genital herpes.
Valcyk®Benta is indicated for the suppression (prevention) of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes.
Valcyk®Benta can reduce transmission of genital herpes when taken as suppressive therapy and combined with safer sex practices (particularly the use of condoms).
Valcyk®Benta is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, following renal transplantation.

CONTRAINDICATIONS

Valaciclovir is contra-indicated in patients with known hypersensitivity to Valaciclovir, aciclovir or any of the ingredients of the preparation.

PRECAUTIONS

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.
Valaciclovir does not cure genital herpes or eliminate the risk of transmission, it is recommended that patients use safer sex practices.
The Valaciclovir dose should be reduced in patients with renal impairment as they are at increased risk of developing neurological side effects.
The results of mutagenicity tests in vitro and in vivo indicate that Valaciclovir is unlikely to pose a genetic risk to humans. Valaciclovir was not carcinogenic nor teratogenic in mice and rats.
Valaciclovir did not affect fertility in male or female rats dosed by the oral route.



PREGNANCY AND LACTATION

There are limited data on the use of Valaciclovir in pregnancy. Valaciclovir should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk. Following oral administration of a 500mg dose of Valaciclovir, peak aciclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal aciclovir serum concentrations. Caution is therefore advised if Valaciclovir is to be administered to a nursing woman. However aciclovir is used to treat neonatal herpes simplex at IV doses of 30 mg/kg/day.

DRUG INTERACTIONS

No clinically significant interactions have been identified. Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations following Valaciclovir administration. Following 1g Valaciclovir, cimetidine and probenecid increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of aciclovir.

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ADVERSE EFFECTS

Gastrointestinal disorders: Common: Nausea. Rare: Abdominal discomfort, vomiting, diarrhoea.
Blood and lymphatic system disorders: Very rare: Thrombocytopenia.
Hypersensitivity reactions: Uncommon: Rashes including photosensitivity, dyspnoea. Rare: Pruritus. Very rare: Anaphylaxis, urticaria, angioedema.
Renal and urinary disorders: Rare: Renal impairment. Very rare: Acute renal failure.
Hepato-biliary disorders: Very rare: Reversible increases in liver function tests, occasionally described as hepatitis.
Psychiatric and nervous system disorders: Common: Headache. Rare: Dizziness, confusion, hallucinations, decreased consciousness. Very rare: Tremor, agitation, ataxia, dysarthria, convulsions, encephalopathy, coma. The above events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors.
Other: Renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia in severely immunocompromised patients, particularly those with advanced HIV disease, receiving high doses (8 g daily) of Valaciclovir for prolonged periods.

DOSAGE AND ADMINISTRATION

Treatment of herpes zoster: The dosage in adults is 1000 mg of Valcyk®Benta to be taken 3 times daily for 7 days.
Treatment of herpes simplex: The dosage in adults is 500 mg of Valcyk®Benta to be taken twice daily. For recurrent episodes, treatment should be for 5 days. For initial episodes, which can be more severe, treatment may have to be extended to 10 days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately the first signs or symptoms appear.
Valcyk®Benta can prevent lesion development when taken at the first signs and symptoms of an HSV recurrence.
Suppression (prevention) of herpes simplex infection: In immunocompetent patients, 500 mg of Valcyk®Benta is to be taken once daily. Some patients with very frequent recurrences (e.g. more than 10 per year) may benefit from taking 500 mg as a divided dose (250 mg twice daily). For immunocompromised patients the dose is 500 mg twice daily.
Reduction of transmission of genital herpes: In immunocompetent heterosexual adult patients with 9 or fewer recurrences per year, 500 mg of Valcyk®Benta to be taken once daily by the infected partner in order to reduce transmission to a sexual partner negative for HSV-2 antibodies. Safer sex practices (particularly condom use) should be maintained, and sexual contact avoided if lesions are present. There are no data on the reduction of transmission beyond 8 months in other patient populations.
Prophylaxis of cytomegalovirus infection (CMV) and disease:
Dosage in adults and adolescents (from 12 years of age): The dosage of Valcyk®Benta is 2g four times a day, to be initiated within 72 hours post-transplant, or as soon as oral medication can be tolerated. This dose should be reduced according to creatinine clearance. The duration of treatment will usually be 90 days.

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Dosage in children: There are no data available on the use of Valcyk®Benta in children.
Dosage in elderly: Dosage modification is not required unless renal function is significantly impaired. Adequate hydration should be maintained.
Hepatic impairment: Dose modification is not required in patients with mild or moderate impaired hepatic synthetic function.
Renal impairment: The dosage of Valcyk®Benta should be reduced in patients with significantly impaired renal function as shown in the table below:

Therapeutic indication	Cl_{cr} ml/min	Valcyk®Benta dosage
Herpes zoster	15-30	1 g twice a day
	less than 15	1 g once a day
Herpes simplex (treatment)	less than 15	500 mg once a day
Herpes simplex prevention (suppression)		
- immunocompetent patients	less than 15	250 mg once a day
- immunocompromised patients	less than 15	500 mg once a day
Reduction of transmission of genital herpes	less than 15	250 mg once a day

For CMV prophylaxis, the dosage of Valcyk®Benta should be reduced in patients with impaired renal function as shown in the table below:

Cl_{cr} ml/min	Valcyk®Benta dosage
75 or greater	2 g four times a day
50 to less than 75	1.5 g four times a day
25 to less than 50	1.5 g three times a day
10 to less than 25	1.5 g twice a day
less than 10 or dialysis	1.5 g once a day

In patients on haemodialysis, the Valcyk®Benta dosage should be administered after the haemodialysis has been performed.

OVERDOSAGE

Acute renal failure and neurological symptoms including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of Valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction. Patients should be observed closely for signs of toxicity. Haemodialysis enhances elimination of aciclovir from the blood and is considered as an option in case of overdosage.

STORAGE CONDITIONS

Store below 25°C.
Keep in original pack in intact conditions.

BPI

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