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Brivudin (Bromovinyl Deoxyuridine)

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Contents

Abstract

▲ Brivudin is an oral thymidine analogue indicated for the early treatment of acute herpes zoster in immunocompetent adults. It has high, selective activity against varicella zoster virus (VZV), inhibiting VZV replication, possibly through competitive inhibition of viral DNA polymerase, or by acting as an alternative substrate to deoxythymidine triphosphate, causing viral DNA strand breakage.

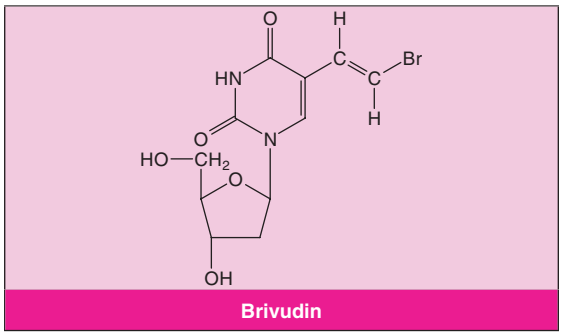
▲ In a large, 7-day, phase III trial in immunocompetent patients with herpes zoster, once-daily brivudin 125mg was significantly more effective than oral acyclovir 800mg five times daily in reducing the mean time from start of treatment to last vesicular eruption, and was as effective as acyclovir at healing lesions and alleviating acute zoster-related pain.

▲ The likelihood of developing post-herpetic neuralgia (PHN) in immunocompetent patients aged ≥50 years was significantly lower with brivudin than with acyclovir.

▲ Brivudin was as effective as oral famciclovir 250mg three times daily in terms of the prevalence of PHN, the time to last vesicular eruption and lesion healing in another large, 7-day, phase III study in immunocompetent patients with herpes zoster.

▲ Oral brivudin is generally well tolerated, with a similar tolerability profile to those of oral acyclovir or famciclovir. Nausea was the most commonly reported adverse event.

Features and properties of brivudin (bromovinyl deoxyuridine)	
Indication	
Early treatment of acute herpes zoster in immunocompetent adults	
Mechanism of action	
Antiviral	Thymidine analogue
Dosage and administration	
Recommended dosage	125mg once daily for 7 days
Route of administration	Oral
Mean steady-state pharmacokinetic profile of brivudin following an oral dosage of 125 mg/day	
Peak plasma concentration	1.7 μg/mL
Time to peak plasma concentration	1h
Volume of distribution	75L
Plasma terminal elimination half-life	≈16h
Adverse events	
Most common	Nausea, other gastrointestinal disorders, headache
Contraindications	
Treatment with 5-FU (fluorouracil) or other fluoropyrimidines	



Herpes zoster (shingles) is a common disease, particularly in the elderly.[1] It is caused by the reactivation of latent varicella-zoster virus (VZV) that has been present on the dorsal root ganglion of the spinal cord since the primary infection of varicella (chickenpox).[2] Herpes zoster is characterised by an acute painful vesicular eruption (zoster-associated pain), and the commonest complication is chronic pain caused by post-herpetic neuralgia (PHN),[1,2] which occurs more frequently in patients aged ≥50 years.[3]

Brivudin (bromovinyl deoxyuridine) is a potent antiviral agent with high and selective activity against VZV.[4] This profile focuses primarily on data relevant to the use of brivudin in immunocompetent patients with herpes zoster.

1. Pharmacological Properties

Pharmacodynamic Properties

- Brivudin is a thymidine analogue that is highly selective for VZV over cellular DNA polymerase.[5,6] It has a high affinity for VZV thymidine kinase,[6] and is sequentially phosphorylated by viral thymidine and thymidylate kinases and cellular kinases to form brivudin triphosphate.[2]
- Once incorporated into VZV DNA, brivudin triphosphate inhibits viral replication, possibly by acting as either a competitive inhibitor of viral DNA polymerase,[2,7] or as an alternative substrate to the natural nucleoside triphosphate deoxythymidine triphosphate,[5,7,8] which leads to viral DNA strand breakage.[2]
- Brivudin triphosphate has a half-life of 10 hours in virus-infected cells,[9] similar to that of penciclovir (9.1 hours) and considerably longer than that of acyclovir [2–3 hours].[9]
- *In vitro*, brivudin was more potent against VZV than acyclovir and penciclovir.[5,7,10,11] In clinical VZV strains, the 50% inhibitory concentration (IC_{50}) for brivudin (0.0033 μmol/L[7] [0.001 μg/mL];[6,12] IC_{50} of 0.0002–0.011 μg/mL in other assays[5,10,11]) was approximately 280- and 1100-fold lower than that for acyclovir (0.93 μmol/L) or penciclovir (3.6 μmol/L) [figure 1].[7]
- A 50% inhibition of viral replication is seen within 1 hour of exposure to brivudin *in vitro*.[6]
- As with other nucleoside analogues, brivudin resistance occurs with viral strains that are thymidine kinase deficient.[6] Such strains generally only emerge when immunodeficient patients are administered chronic antiviral therapy. Resistance to brivudin when administered as a 7-day course in immunocompetent patients with herpes zoster (the approved indication) is, therefore, unlikely.[6]
- Brivudin has low cytotoxicity *in vitro*, and hepatic and renal toxicity *in vivo* was only demonstrated at dosages >25-fold higher than that recommended

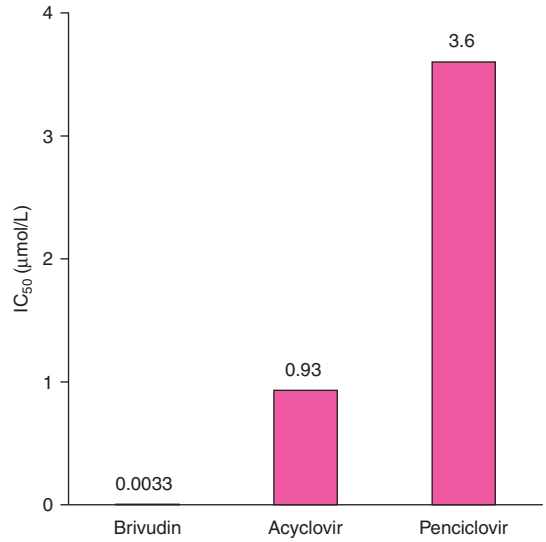


Fig. 1. IC_{50} of selected anti-varicella-zoster virus (VZV) compounds in human embryonic lung cells for clinical strains of VZV.[7] **IC_{50}** = concentration required to reduce viral plaque formation by 50%.

in humans.[13] The carcinogenicity observed in a long-term study in rats is not due to genotoxic properties, but is related to cytotoxic induction of regenerative hepatocellular proliferation following chronic exposure to very high dosages (17-fold higher than the recommended dosage in humans) of brivudin over a 2-year period. Thus, it does not reflect any risk for the lower-dose, short-term treatment in humans.[9,14]

Pharmacokinetic Properties

Published pharmacokinetic data for oral brivudin 125mg in healthy volunteers or patients with herpes zoster are not available. Data in this section are from the manufacturer's summary of product characteristics[6] and a study that examined the effects of oral brivudin 250–750mg on the pharmacokinetics of 5-FU (fluorouracil) in 12 cancer patients.[15]

- Brivudin is almost completely absorbed after oral administration. Steady-state concentrations are achieved after 5 days of once-daily administration.[6] The mean maximum plasma concentration (C_{max}) at steady state (1.7 μg/mL) is achieved 1 hour after administration of once-daily oral brivudin 125mg,[6] and is 1700-fold greater than the *in vitro* IC_{50} versus VZV.[6,12]
- The mean minimum plasma concentration at steady state is 0.06 μg/mL[6] (60-fold greater than the *in vitro* IC_{50} versus VZV).[5-7,10-12] Absorption of the drug is not significantly affected by food.[6]
- The pharmacokinetics of brivudin are linear within a dose range of 31.25–125mg. Once steady state is achieved, there is no further evidence of accumulation.[6]
- The bioavailability of brivudin after absorption is low (≈30% of an oral dose), because of extensive first-pass metabolism.[6] Brivudin is widely distributed in tissues, with a volume of distribution of 75L. It is highly bound (>95%) to plasma protein,[6] and is not displaced by concomitantly administered agents such as analgesics, cardiac glycosides, cytostatics or other antiviral agents.[13]
- After absorption, brivudin is rapidly and completely metabolised to bromovinyluracil (which has no antiviral activity and is the only metabolite detected in plasma) via the enzyme pyrimidine phosphorylase, mainly in the liver.[6] It is then further metabolised to urea-based compounds, including uracil acetate, which is the main polar metabolite detected in the urine.[6]
- Renal elimination predominates, with 65% of a dose eliminated in the urine as metabolites, and <1% as the unchanged drug.[6] Approximately 21% of a dose is excreted in the faeces.[13] Total body clearance is 240 mL/min, and the plasma terminal elimination half-life ($t_{1/2}\beta$) is approximately 16 hours.[6] The total body clearance and $t_{1/2}$ values for bromovinyluracil are similar to those of the parent compound (no data reported).[6]
- The pharmacokinetics of brivudin (C_{max}, area under the plasma concentration-time curve [AUC], $t_{1/2}$) in the elderly, and in patients with moderate or severe renal failure (creatinine clearance of 26–50 mL/min/1.73m^2 [1.6–3.0 L/h] or <25 mL/min/1.73m^2 [<1.5 L/h]) or with liver failure (Child-Pugh Class A–B) are essentially similar to those in healthy volunteers, and dosage adjustment is not required in these patient groups.[6]

Drug Interactions

- Bromovinyluracil, the main metabolite of brivudin, irreversibly inhibits dihydropyrimidine dehydrogenase (DPD), the enzyme that regulates the metabolism of natural nucleosides, such as thymidine, and that of pyrimidine derivatives, including the fluoropyrimidine 5-FU.[6]
- Coadministration of brivudin and 5-FU increases the systemic exposure to 5-FU and increases its toxicity.[6] In a study in cancer patients, the administration of oral brivudin 250–750mg followed by intravenous 5-FU 1.5–5 mg/kg increased the AUC of 5-FU approximately 5- to 15-fold compared with that with 5-FU alone.[15]
- A study in healthy adults who received oral brivudin 125mg once daily for 7 days showed that DPD activity was fully restored 18 days after administration of the final dose of brivudin.[6] Consequently, the coadministration of brivudin and fluoropyrimidine derivatives, or administration of these

agents within 4 weeks of each other, is contraindicated (section 4).[6]

- Brivudin has not been shown to interact with any other drugs, and it has no effect on cytochrome P450 enzymes.[6]

2. Therapeutic Efficacy

The efficacy of brivudin for the early treatment of acute herpes zoster has been compared with that of acyclovir[4,16] and famciclovir[17] in two large, clinical trials in immunocompetent adults. Comparisons with acyclovir are fully published,[4,16] and include a double-blind, post-study survey[16] on PHN in patients aged ≥50 years who participated in two randomised, clinical herpes zoster trials, one of which was the large trial[4] that is the main focus of this section. The comparison with famciclovir is available as an abstract and poster.[17]

Comparison with Acyclovir

A large, randomised, double-blind, double-dummy, multicentre trial compared the efficacy of oral brivudin and oral acyclovir in 1227 adult (aged ≥18 years) herpes zoster patients.[4] Patients with ophthalmic or CNS complications, visceral dissemination, or evidence of immunodeficiency were excluded from the study. Patients with renal or hepatic impairment and pregnant or nursing women were also excluded.[4]

Patients received oral brivudin 125mg once daily (intent-to-treat [ITT] population; n = 612) or oral acyclovir 800mg five times daily (ITT; n = 613).[4] Treatment was started within 48 hours of the first eruption of vesicles and continued for 7 days. Approximately 90% of patients suffered from zoster-associated pain at baseline.[4]

The primary efficacy endpoint was the time from start of treatment to last eruption of herpes zoster vesicles.[4] Secondary endpoints included the time from start of treatment to start of vesicle crusting, complete crusting and complete loss of crusts, time from start of treatment to cessation of acute zoster-associated pain, pain intensity and use of analgesic medication.[4] Patients recorded the intensity and type of pain (using a 6-point scale where 0 = no pain and 5 = unbearable pain) and the use of analgesic medications throughout the study.[4] Results reported are for the ITT population.

- Brivudin achieved significantly greater efficacy than acyclovir in immunocompetent herpes zoster patients.[4] A greater reduction in the mean time from start of treatment to last eruption of new herpes zoster vesicles was seen with brivudin than with acyclovir (13.7 vs 17.7 hours; $p = 0.014$).[4] Furthermore, in a subgroup of patients aged ≥50 years (n = 755), brivudin was superior to acyclovir in terms of the primary endpoint (15.3 vs 18.8 hours; $p = 0.022$).[4]

- Brivudin was as effective as acyclovir for the healing of zoster lesions.[4] The mean times from start of treatment to start of crusting of lesions (65.3 vs 63.3 hours), or to full crusting (137.8 vs 140.7 hours) or loss of crusts (360.3 vs 350.2 hours) with brivudin or acyclovir were equivalent (p-values for noninferiority of 0.004, <0.001 and 0.002, respectively).[4]

- The alleviation of acute zoster-associated pain was similar after treatment with brivudin or acyclovir.[4] The mean time from start of treatment to cessation of acute zoster-associated pain with brivudin was equivalent to that with acyclovir (266.0 vs 258.4 hours; p-value for noninferiority of 0.001), and the patients' mean score for the intensity of acute pain during the study was 1.25 in both treatment groups.[4]

- Use of analgesic medications, which was similar in the brivudin and acyclovir treatment groups at baseline (17.3% vs 14.2%), increased to a maximum at day 2 after treatment initiation (33.3% vs 35.2%) and decreased thereafter.[4]

- The overall incidence of chronic PHN (defined as pain of any intensity after healing of acute herpes zoster) in patients aged ≥50 years (n = 608) who participated in the double-blind survey study was significantly lower in brivudin than in acyclovir recipients (32.7% vs 43.5%; $p = 0.006$; odds ratio 1.6) [figure 2].[16] Nevertheless, the mean duration of PHN (173 days with brivudin and 164 days with

acyclovir), and the type and pattern of PHN did not differ between the two treatment groups.[16]

Comparison with Famciclovir

Limited data are available from a large, randomised, double-blind, multicentre study in which the efficacy of brivudin 125mg once daily was compared with that of famciclovir 250mg three times daily for 7 days in 2027 herpes zoster patients aged ≥50 years. Patients were followed for up to 9 months.[17] Treatment was started within 72 hours of rash onset and all patients had pain at baseline.[17]

- Brivudin was as effective as famciclovir, evidenced by an equivalent prevalence of PHN (the primary endpoint) in the ITT population (n = 1954) at 3 months after the start of treatment (11.1% vs 9.2%; noninferiority p-value of 0.01).[17] The median duration of PHN in the per-protocol population (number of patients not stated) was numerically shorter with brivudin than famciclovir, although the difference was not statistically significant (46.5 vs 58.9 days).[17]

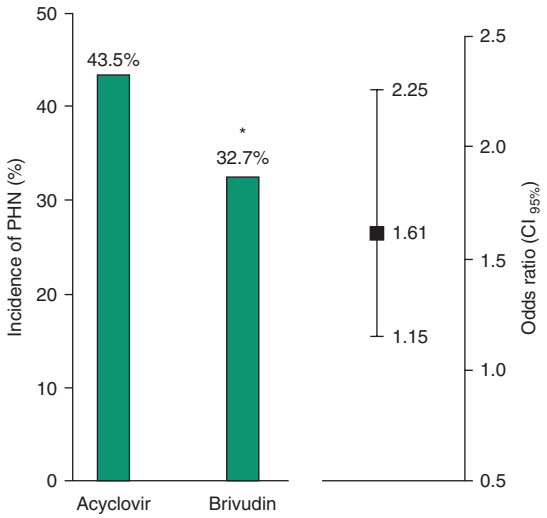


Fig. 2. Overall incidence of post-herpetic neuralgia (PHN) after treatment with brivudin or acyclovir for herpes zoster. Results from a group of patients aged ≥50 years who had received oral brivudin 125mg once daily (n = 309) or oral acyclovir 800mg five times daily (n = 299) for 7 days in two randomised, double-blind clinical trials, and who completed a double-blind, post-study survey (reproduced from Wassilew and Wutzler,[16] with permission from Elsevier). **CI** = confidence interval; * p = 0.006.

- Moreover, there were no significant differences between the two ITT treatment groups (n = 2025) for the time to last vesicular eruption (data not reported), or to healing of zoster lesions (mean time to complete crusting of lesions [6.6 vs 6.8 days] or to loss of crusts [16.9 vs 17.0 days]).[17]

Immunocompromised Patients

Although brivudin is contraindicated in immunocompromised patients (section 4),[6] older studies performed in the early 1980s evaluated the efficacy of brivudin in this patient group. A small, randomised, double-blind, double-dummy, multicentre trial that compared the efficacy of oral brivudin and intravenous acyclovir in 48 adult (aged >16 years) patients with underlying malignant disease and herpes zoster rash of <72 hours' duration has been published.[18] Patients received oral brivudin 125mg every 6 hours (n = 24) or intravenous acyclovir 10 mg/kg as a 1-hour infusion every 8 hours (n = 23) for 5 days.[18]

Patients who were severely immunocompromised because of their underlying disease, those with serum creatinine levels >1.0 mmol/L or a creatinine clearance <1 mL/sec (3.6 L/h), those receiving concomitant treatment with immunoglobulins or those with a history of drug allergies were excluded.[18]

- Oral brivudin was as effective as intravenous acyclovir with respect to new lesion formation at day 3 (13% vs 13% of patients), increase in primary rash area (13% vs 17%), development of (13% vs 17%) or severity of (data not reported) cutaneous dissemination, mucous membrane (4% vs 9%) or visceral organ involvement (0% vs 0%) [all after day 1], or time to complete crusting or healing of the primary lesions (83% vs 78% on day 12).[18]
- According to results of a subjective questionnaire, similar proportions of patients in each treatment group reported an improvement in general feeling between days 3 and 4.[18] However, the mean reported pain score for days 1, 2 and 5 was significantly lower with brivudin than with acyclovir ($p \leq 0.03$).[18]

3. Tolerability

This section provides a brief summary of tolerability data from the clinical trials that evaluated the efficacy of brivudin in immunocompetent patients with herpes zoster (section 2).

- Oral brivudin was well tolerated in clinical trials and had a similar tolerability profile to those of acyclovir and famciclovir.[4,17] The incidence of adverse events with a definite, possible or probable relationship to treatment in immunocompetent patients receiving brivudin or acyclovir was similar (7.7% vs 10.0%).[4] Potential treatment-related adverse events occurred in similar percentages of brivudin or famciclovir recipients (11.8% vs 10.1%).[17]
- The most common adverse event reported with brivudin is nausea (2.1% of >3900 patients).[6] Gastrointestinal disturbances (nausea [2.6% vs 2.1%], abdominal pain [0.8% vs 0.7%] and vomiting [0.5% vs 1.1%]) and headache (1.0% vs 1.1%) were the most common adverse events that were potentially related to brivudin treatment in the clinical comparison with acyclovir.[4]

4. Dosage and Administration

Oral brivudin is indicated for the early treatment of acute herpes zoster in immunocompetent adults.[6] The recommended dosage is a single treatment cycle consisting of one brivudin 125mg tablet once daily for 7 days. Treatment should begin as early as possible, either within 72 hours of the first skin manifestations or within 48 hours of the first blister appearing, and should be taken at approximately the same time each day.[6] It is contraindicated in immunocompromised patients, including those receiving cancer chemotherapy or immunotherapy.[6]

There is a boxed warning regarding the coadministration of brivudin with 5-FU or other fluoropyrimidine derivatives (such as floxuridine, tegafur, capecitabine or combination products containing these active substances, and other fluoropyrimidines, including flucytosine). This is because the inhibition of DPD (the enzyme that regulates the metabolism of pyrimidine derivatives) by the major metabolite of brivudin (section 1) causes accumulation and increased toxicity of these drugs.[6] In addition, an interval of at least 4 weeks is required between treatment with brivudin and treatment initiation with medications containing a fluoropyrimidine derivative (section 1). Prior to treatment with medications containing a fluoropyrimidine derivative, DPD enzyme activity should be established in patients who have recently received brivudin.[6]

5. Brivudin: Current Status

Brivudin is currently available in Austria, Estonia, Germany, Italy, Latvia, Lithuania, Portugal, Romania, Slovac Republic, Spain, Switzerland and Turkey for the early treatment of acute herpes zoster in immunologically competent adults and has been registered in many other countries.

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