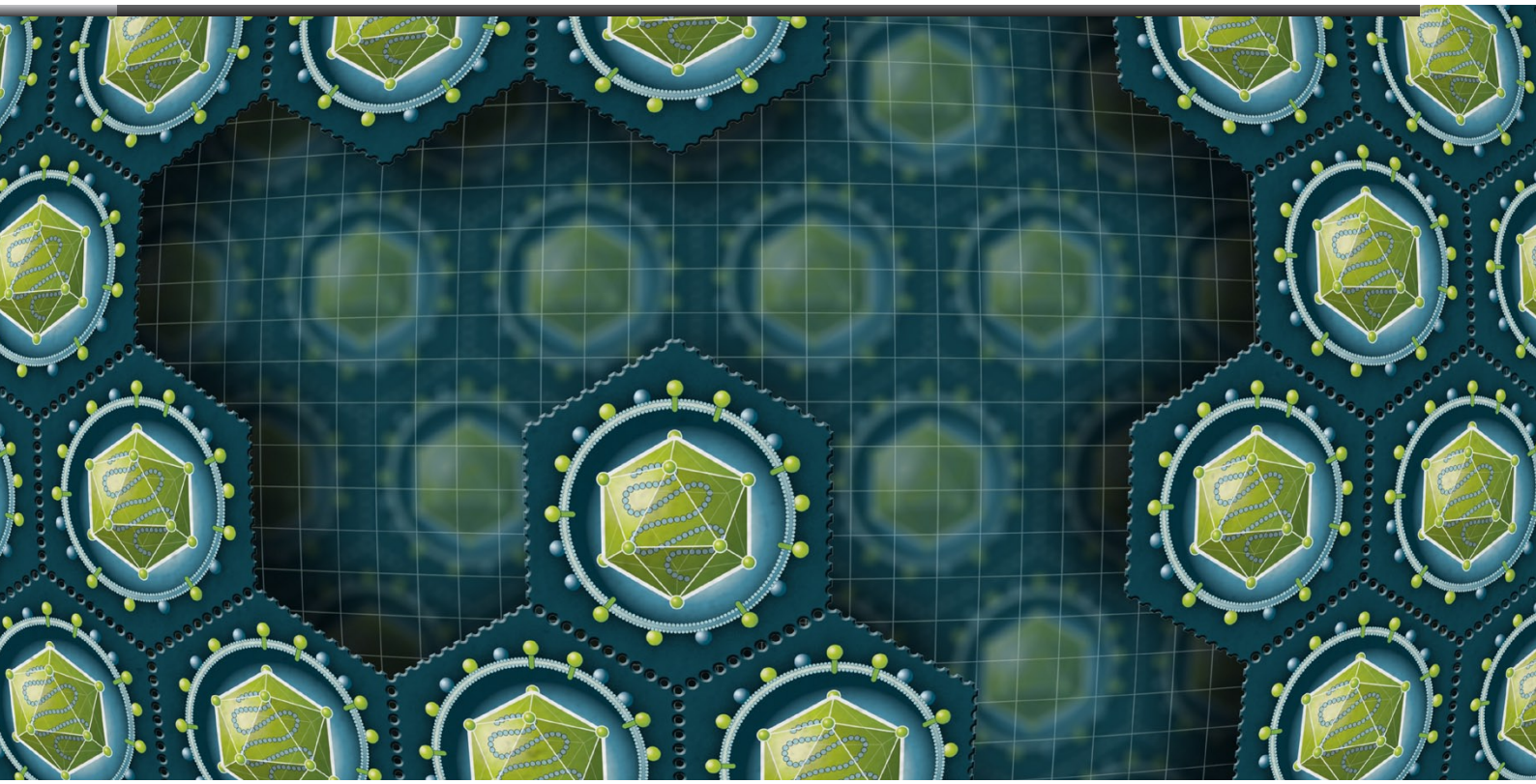

Valaciclovir – a first line antiviral medicine

Valaciclovir is an antiviral medicine which can be used for the treatment of Herpes simplex infections and herpes zoster. As of 1 March, 2016, Special Authority approval is no longer required. Valaciclovir is as effective as aciclovir across the same range of indications, and has a simpler dosing regimen which may improve patient adherence.

Valaciclovir is now available without restriction

Valaciclovir and aciclovir are antiviral medicines that interfere with replication of Herpes viruses including Herpes simplex and Varicella zoster.[1] General practitioners in New Zealand are more likely to be familiar with aciclovir than valaciclovir as it has been fully subsidised and used in clinical practice for longer.

Valaciclovir consists of a valine amino acid attached to an aciclovir molecule. Following administration, the amino acid is cleaved and valaciclovir is converted into aciclovir. Due to increased bioavailability oral valaciclovir can be taken less frequently than oral aciclovir, e.g. two to three times daily instead of five times daily.[2, 3]

Prior to 1 March, 2016, Special Authority approval was required for patients to receive subsidised treatment with valaciclovir, 500 mg tablets; the Special Authority criteria has been removed and valaciclovir is now available without restriction for:

- The treatment of first and recurrent episodes of genital herpes
- Suppression of genital herpes recurrences
- The treatment of herpes zoster

This article provides clinical guidance for the use of valaciclovir in patients with each of these conditions.

Prescribing valaciclovir

Dosing and duration of treatment

The recommended doses, frequency and duration of valaciclovir treatment differ according to the condition being treated. For prescribing information refer to the specific conditions below or to the New Zealand Formulary (NZF).

For more information see: **www.nzf.org.nz/nzf_3443**

Adverse effects and cautions for prescribing

The adverse effects most commonly experienced by patients taking valaciclovir are headaches, rhinitis and flu-like symptoms. These symptoms are usually mild to moderate, although some patients may discontinue treatment as a result. In randomised controlled trials the incidence of these symptoms is only slightly higher than in patients taking placebo.[4, 5]

Patients taking valaciclovir should be advised to maintain adequate hydration. There have been isolated case reports of older patients or patients with severely reduced renal function developing acute kidney injury following treatment with 1 g three times daily, for as little as one day.[6, 7]

Rarely, valaciclovir use can cause aciclovir-induced neurotoxicity.[6] Symptoms of aciclovir-induced neurotoxicity include hallucinations, involuntary movements and characteristic delusions of death: either that the patient or someone else is going to die or has already died.[8] Withdraw treatment in patients suspected of having aciclovir-induced neurotoxicity, especially if they have reduced renal function.[8]

Dose adjustments are required for some patients

Reduced dosing is required in patients with renal impairment. Dose adjustments are required in patients with renal impairment, as the half-life of valaciclovir is extended from two to three hours in healthy individuals, up to 14 hours in patients with end-stage renal failure.[1, 8]

Immunocompromised patients require an increased dose and longer duration of valaciclovir treatment.[2, 9]

For specific information on dose adjustments in patients with renal impairment see: **www.nzf.org.nz/nzf_3443**

Valaciclovir for the treatment of genital herpes

Without treatment the symptoms of genital herpes can last for up to three weeks.[3] Treatment with valaciclovir or aciclovir reduces the time to healing, the severity and duration of symptoms and viral shedding.[1] In one large randomised controlled trial the median time to symptom resolution for patients taking either valaciclovir or aciclovir was approximately nine days; with almost all patients having symptom resolution and lesion healing by two weeks.[10]

Oral valaciclovir, 1000 mg, twice daily, produces the same clinical benefit as oral aciclovir, 200 mg, five times daily, when taken for the same duration, with similar duration of symptoms, pain, viral shedding and time to healing.[10]

Continuous valaciclovir treatment can reduce the incidence of symptomatic episodes

Patients who regularly experience recurrent genital herpes, e.g. six episodes or more per year, may trial preventative treatment to reduce the impact of the disease and to provide a sense of control over the disease process.[3, 11] There is evidence that continuous treatment with valaciclovir can reduce the number of recurrent episodes of genital herpes by approximately 60%.[11] The clinical threshold at which continuous treatment with valaciclovir could be offered is influenced by the patient's ability to tolerate recurrences and their willingness to adhere to treatment.[9]

How to prescribe valaciclovir for the treatment of genital herpes

Valaciclovir dosing recommendations* differ depending on the intended use:[3, 9]

- **For first episodes:** valaciclovir 500 mg, twice daily, for seven days, or longer if new lesions appear or lesions are not fully healed (consider 1000 mg, twice daily, for seven to ten days in immunocompromised patients)
  - All patients with suspected first episodes of genital herpes should receive empiric treatment with valaciclovir, without waiting for confirmatory test results (see: "The role of testing in the diagnosis and treatment of genital herpes", over page)
- **For recurrent episodes (episodic treatment):** valaciclovir 500 mg, twice daily, for three days
  - Consider providing the patient with a prescription to be used as soon as symptoms begin
- **For prevention of recurrences (suppressive treatment):** valaciclovir 500 mg, daily
  - Only recommended if HSV confirmed on testing
  - Withdraw treatment every 6–12 months to reassess the recurrence frequency; consider restarting treatment after two recurrences
  - Dosing may be increased to 500 mg, twice daily, or 1 g, once daily, for patients who continue to experience multiple recurrences (unapproved dose)

* Valaciclovir doses in this article may differ from those in the Medicine Data Sheet and the NZF. This dosing information is endorsed by the New Zealand Herpes Foundation.

Valaciclovir for pregnant women or women planning pregnancy

Transmission of the herpes virus to neonates during delivery is a potentially serious event. Women who have had symptomatic herpes before pregnancy can be assured that the risk of passing the infection on to their baby is very small (approximately 0.05%), if they have no signs or symptoms at the time of delivery.[3] Suppressive therapy to avoid a recurrence

The role of testing in the diagnosis and treatment of genital herpes

Testing should be requested for patients with first episodes of genital herpes (and atypical recurrences) to confirm the diagnosis and determine the type of virus involved. This can provide prognostic information, e.g. HSV-2 is associated with more frequent recurrences of genital herpes than HSV-1 infections. Approximately 70–90% of patients who have symptomatic HSV-2 genital infections and 20–50% of patients with genital HSV-1 infections experience a recurrence within the first year.[12]

After removing the covering tissue with a needle or scalpel, swabs are taken from the base of the lesion to collect virus-infected cells and vesicular fluid. Polymerase chain reaction (PCR)-based detection is now the preferred method for herpes virus testing. If this is not available viral culture is an alternative method of testing; culture has a higher specificity, but lower sensitivity, than PCR-based detection and usually takes longer to receive a result.

Arrange a follow-up appointment at five to seven days for patients with test results positive for genital herpes to provide counselling and future lifestyle advice (see: "Advice for patients with genital herpes").

Herpes virus serology, i.e. testing for the presence of antibodies to HSV-1 or HSV-2, is not recommended as a routine test. Herpes antibodies typically take two to six weeks to develop and sometimes longer. Patients presenting with new infections are therefore likely to test negative for antibodies. A positive serology result may indicate that the patient has previously had an asymptomatic infection but would not change how they are managed. Serology may be useful in specific circumstances, such as to test whether a pregnant woman has antibodies to herpes virus if their partner develops symptomatic genital herpes during the pregnancy (see: "Valaciclovir for pregnant women or women planning pregnancy").[3]

near the time of delivery can be considered in women with a history of genital herpes; consultation with an obstetrician or gynaecologist is recommended.[3]

The greatest risk of neonatal transmission occurs when a woman has a first episode of symptomatic herpes near or at the time of delivery. For women who develop symptomatic genital herpes during pregnancy, particularly during the third trimester, consultation with an obstetrician or gynaecologist is recommended. For women who develop symptomatic genital herpes during the first or second trimester, standard treatment with antiviral medicines and vaginal delivery is possible. Delivery by caesarean section is recommended for women with a first episode during the third trimester.[3] A first episode of herpes symptoms during pregnancy may not be a new infection, due to changes in immune function, this may be the first symptomatic episode in a woman previously infected.[3]

If a pregnant woman, without a prior history of symptomatic genital herpes, has a partner with a history of herpes symptoms, serological testing of both partners may be beneficial. If the male partner is seropositive for HSV-2 infection and the female seronegative, suppressive treatment of the male partner could reduce the risk of transmission; this regimen has been shown to reduce the risk of transmission between partners by approximately 50%.[3, 9] The use of valaciclovir to prevent transmission in this way is an unapproved indication.

Advice for patients with genital herpes [3, 9, 13]

Inform patients that there is no cure for herpes virus infection; valaciclovir can reduce the severity of symptoms and the incidence of recurrences, but does not clear the infection.

Transmission risk is highest during recurrences and patients should avoid sexual contact while they have symptoms, even if they are taking valaciclovir. Transmission can also occur when people are asymptomatic. Infected people will need to discuss the approach they wish to take if they want to avoid transmission to an uninfected partner; condoms can reduce but not eliminate the risk of transmission.

Herpes recurrences may be preceded by symptoms such as tingling, burning or pain in the anogenital region, which may extend to hips or legs for two to five days before visible lesions develop. Patients should begin taking valaciclovir to treat a recurrence at the onset of these symptoms.

Salt baths may relieve pain and improve the healing of lesions, e.g. half a cup of salt in a bath. Patients often experience pain during urination and application of lignocaine gel a few minutes prior to urination may lessen discomfort. Topical lignocaine products are not subsidised for this indication. Sensitisation to topical lignocaine occurs rarely but patients should be aware of the possibility of irritant hypersensitivity.

Patient information and support is available from:
www.herpes.org.nz

Valaciclovir for the treatment of herpes zoster (shingles)

Herpes zoster, also known as shingles, is caused by reactivation of latent Varicella zoster virus in individuals who have previously had varicella, and usually occurs in people aged 40 years and over.[14]

Patients with herpes zoster often describe an itching or burning, shooting pain which precedes a characteristic rash by three to four days. Typically, patients display a unilateral rash with a distribution corresponding to the affected dermatome.[14] Diagnosis can usually be made on the basis of this dermatomal rash with accompanying pain, without the need for further investigation. Testing may be necessary if there is uncertainty, e.g. to differentiate between Herpes simplex infection and herpes zoster or if herpes zoster without rash (zoster sine herpete) is suspected.

Post-herpetic neuralgia occurs in 10–18% of patients with herpes zoster and causes ongoing pain after the resolution of other symptoms and signs.[14]

Valaciclovir is more effective at reducing pain due to herpes zoster than aciclovir

Antiviral medicines reduce the severity and duration of acute pain for patients with herpes zoster; valaciclovir may result in improved symptoms compared with the use of aciclovir. A study of over 1,000 patients, using comparable doses of valaciclovir or aciclovir, reported that resolution of pain was on average 25% quicker for patients taking valaciclovir than patients taking aciclovir (p=0.001). The duration of cutaneous symptoms and signs was similar for both groups of patients.[15]

Valaciclovir is unlikely to prevent post-herpetic neuralgia, as this has not been observed in studies of aciclovir for the treatment of herpes zoster, although clinical trials assessing this end-point with valaciclovir have not been conducted.[16]

How to prescribe valaciclovir for the treatment of herpes zoster:[17]

- Valaciclovir, 1g, three times daily, for seven days to reduce the pain associated with symptomatic episodes; lower doses are required in patients with reduced renal function, see: **www.nzf.org.nz/nzf_3443**
- Immunocompromised patients should continue dosing for at least two days after lesions have crusted, which may result in treatment for longer than seven days

Red flag: Patients with herpes zoster and signs of involvement of the ophthalmic branch of the trigeminal nerve (herpes zoster ophthalmicus) should be discussed with an ophthalmologist.[18] Herpes zoster ophthalmicus can result in serious sequelae including keratitis, uveitis, glaucoma and blindness.[2]

Advice for patients with herpes zoster

Advise patients with herpes zoster to avoid physical contact with others to reduce the risk of transmission, especially infants aged one year and under, pregnant women and immunocompromised people. Lesions should be kept clean and dry and can be covered with a dressing without an adhesive backing.[2] Patients should refrain from scratching the rash to reduce transmission and scarring.

Following the resolution of cutaneous symptoms and signs patients may experience ongoing pain that may resolve over months to years, but can often continue despite treatment.[19] In clinical trials in patients with post-herpetic neuralgia, fewer than half of patients treated with analgesia have a 50% or greater reduction in pain.[19] Treatment options in primary care for chronic pain due to herpes zoster include topical capsaicin creams (0.075%), paracetamol, or for more severe pain, medicines such as tricyclic antidepressants or anticonvulsants may be of benefit.[20]

For further information on the diagnosis and management of herpes zoster, see: "The diagnosis and management of herpes zoster and its complications", BPJ 59 (Mar, 2014).

Vaccination reduces the risk of developing herpes zoster

Zoster vaccine (Zostavax, a live attenuated vaccine) is recommended but not subsidised in New Zealand for people aged 50 years and over.[14]

Vaccination can prevent the development of herpes zoster by approximately 50% and reduce the incidence of post-herpetic neuralgia by approximately 40%.[21, 22] Patients aged 60–69 years may receive a greater benefit from vaccination (64% reduction in risk) than patients aged 70 years and over (36% reduction in risk).[21] The number-needed-to-treat is 50, in patients aged 60 years and over, for vaccination to prevent one case of herpes zoster. Adverse effects include mild to moderate injection site reactions.[21] The vaccine is effective for at least five years, but it is not known how long protection lasts beyond this time and if, or when, repeat vaccination is necessary.[14]

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Problematic cold sores (herpes labialis)

Most patients with herpes labialis experience no more than one recurrence per year, although 5–10% of patients experience six or more episodes per year.[23] The majority of patients who have recurrences will have episodes that are not sufficiently problematic for them to seek medical attention. Triggers for recurrence include sun exposure, stress, hormonal fluctuations and minor trauma or cosmetic procedures.[23]

For patients who present with particularly painful or extensive cold sores, clinicians may advise the use of a topical product containing aciclovir (available unsubsidised in pharmacies and supermarkets) or consider prescribing oral valaciclovir:

- Topical aciclovir 5% creams have been shown to produce statistically significant but clinically small effects in patients with cold sores, reducing pain and symptoms by approximately half a day[24]
- Oral valaciclovir, 2 g twice daily for one day, reduces healing time by approximately one day.[24] However, this is an unapproved use of oral valaciclovir.[17]

There is little evidence to support the use of antiviral medicines to prevent recurrences of cold sores in patients without underlying conditions, e.g. immunocompromised patients.[23] For patients with recurrent cold sores, wearing sunscreen on the affected area during periods of remission may reduce recurrences.[23] Stress management techniques may also be beneficial as recurrence of cold sores has been associated with periods of psychological stress. Recent research has identified a molecular mechanism by which stress signals in neurons can induce reactivation of the Herpes virus.[25]

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