THE NORTHERN HOSPITAL

# VALACICLOVIR

*Wisteria Table Lamp, c. 1902, leaded glass, bronze and copper. Louis Comfort Tiffany and Clara Driscoll.*

*One of Tiffany's iconic lamps, this object comprises nearly, 2000 pieces of individually selected and carefully cut glass. It is believed that Tiffany was responsible for the design, but it was Clara Driscoll, the head of his glass-working team, who actually created the lamp. In blues and mauves, the glass pieces are shaped to resemble tiny petals, replicating a wisteria in bloom. These delicate cascading petals contrast with the lamp's solid bronze stand that is shaped like a thick trunk with spreading roots at the base. Tiffany and Driscoll were both inspired by their love of nature, European developments in Art Nouveau, the Aesthetic Movement, and Japanese design styles.*

*Having set up his glass-making company in 1885 to produce stained glass windows, Tiffany patented his iridescent Favrile glass a decade later, expanding to include coloured glass lampshades a year after that. His plan was to take advantage of the new electric light bulbs that Edison had made commercially viable in 1880. Electric light radiated with seemingly magical effects from within Tiffany's coloured glass shades. The colours of Favrile glass were variegated and the light emphasised this individuality. Created in a similar way to Tiffany's stained glass windows, this lampshade was made with a template. The small petal shapes, were traced onto the glass then cut out using specialist pliers. Once all the pieces were cut, they were painstakingly fused together with strips of copper, which also became an integral part of the design.*

*Dexterous, sensitive to colour and with an eye for detail, Driscoll created many of Tiffany's most successful lampshades, and she managed a large department of young women who became known as the "Tiffany Girls". Although her name was not acknowledged on the lamps she designed - no individual worker was named on Tiffany products - Tiffany made it clear how much he admired her work, and they shared an appreciation of vibrant colour combinations. As an indication of how much Tiffany valued her it is believed that Driscoll was the highest paid woman in America at that time.*

*Susie Hodge, 50 Art Nouveau Works You Should Know, Prestel, 2015*

*It is a recurring motif of the modern age that great discoveries, or great talents are hidden behind large corporations or powerful individuals. Many working behind the scenes are never given due recognition for their genius, particularly in centuries gone by, in regards to women who worked in male dominated societies, Ms. Clara Driscoll of Tiffany's being a classic example. The story behind the development of the antibacterial drug penicillin by Alexander Fleming and Howard Florey is well known. Both are, justifiably, immensely famous. Who today, however knows the names of the people most responsible for the development of the first anti-viral agent, acyclovir? The development of this agent in truth required contributions from many brilliant but faceless scientists behind the monolithic facades of modern day "Big Pharma"; however if any one individual can be credited with the single most important discovery that allowed for the development of the first anti-viral drug it would be Gertrude B. Elion. Though neither women became "household" names of the rank of Fleming or Florey both Clara Driscoll and Gertrude Elion did at least eventually gain some reward for the brilliant work they performed in their respective Arts. While Clara was at one time reportedly the highest paid woman in America, Gertrude would be belatedly awarded the Nobel Prize for Physiology or Medicine in 1988.*

# VALACICLOVIR

## Introduction

**Valaciclovir** is a **prodrug** preparation of acyclovir.

**Acyclovir (or aciclovir)** is a purine (guanine) nucleoside synthetic analogue antiviral agent which is active against herpes simplex (HSV) types I and II and varicella zoster virus (VZV).

It has several advantages over acyclovir:

1. It has a longer duration of action, and so can be given less frequently.

2. There is some evidence that famciclovir (as well as valaciclovir) is more effective than acyclovir in reducing acute pain in cases of herpes zoster. [1]

3. It has better **oral bioavailability** than acyclovir:

    - Valaciclovir is converted in the liver to acyclovir and achieves plasma concentrations 2 - 4 times that of equivalent oral doses of acyclovir.

4. It has better activity against CMV

Its principal disadvantages include:

1. Unlike acyclovir, it can only be given orally and not intravenously.

2. There is limited experience with its use in pregnancy, (and so acyclovir is preferred in pregnancy

## History

**Acyclovir** was the first major anti-viral drug. Its development, in the mid 1970s, was based largely on the brilliant work of **Gertrude B. Elion** who was an American biochemist and pharmacologist. Her work stemmed from the earlier studies of others on an obscure large shallow water Caribbean sponge, ***Tectitethya crypta*** (formerly known as ***Cryptotheca crypta***).

Lacking an immune system, as we know it, sponges evolved an ability to synthesize a variety of unusual compounds for protection against viral infection. C-nucleosides isolated from the Caribbean Cryptotethya crypta, were the basis for the synthesis of a range of anti-viral agents which included the first anti-retroviral drug zidovudine (AZT) and the first anti- herpes agent acyclovir.

Gertrude B. Elion was jointly awarded the 1988 Nobel Prize in Medicine, with Sir James W. Black and George H. Hitchings for her work which directly led to the development of the first anti-viral drugs.

Valaciclovir was introduced into clinical practice in 1995.

## Chemistry

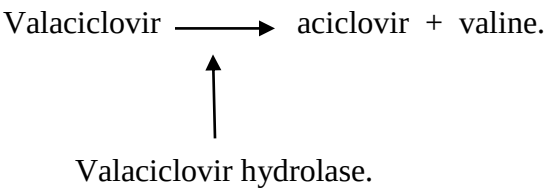
Two of the five bases in nucleic acids, are **purine** derivatives, **adenine and guanine.**

Three of the five bases in nucleic acids are **pyrimidine** derivatives: **cytosine, thymine, and uracil.**

Acyclovir is a synthetic acyclic **purine** (guanine) **nucleoside analogue.**

Valaciclovir is the L-valine ester of aciclovir.

It is converted in the liver as follows:




## Classification

The *guanine* analogue antiviral agents include:

1. Acyclovir
2. Famciclovir:
    - Famciclovir is converted in vivo to the active penciclovir.
3. Ganciclovir
4. **Valaciclovir:**
    - Valaciclovir is converted in the liver to acyclovir
5. Valganciclovir:
    - Valganciclovir is converted to ganciclovir in the intestinal wall and liver

## Preparations

Valaciclovir hydrochloride monohydrate as:

Tablets:

- 500 mg
- 1 gram.

## Mechanism of Action

Following phosphorylation by viral and cellular enzymes, guanine analogues inhibit viral DNA polymerase and so DNA synthesis.

Acyclovir needs to be phosphorylated to the active compound, acyclovir triphosphate, in order to become active against the virus.

Such conversion is very limited in *normal* cells and in addition *cellular* DNA polymerase is not very sensitive to the active compound.

However, in *infected* cells HSV or VZV coded thymidine kinases *facilitate the conversion of acyclovir to acyclovir monophosphate*, which is then converted to acyclovir triphosphate by cellular enzymes.

Acyclovir triphosphate acts as an inhibitor of, and substrate for, the *herpes specified* DNA polymerase, preventing further viral DNA synthesis.

## Pharmacodynamics

Valaciclovir has antiviral activity against:

1. Herpes simplex viruses (HSV types 1 and 2)
2. Varicella zoster virus (VZV).
3. CMV

Cross-resistance may occur between guanine analogues agents due to their similar mechanisms of action and activation pathways.

## Pharmacokinetics

### *Absorption:*

- Valaciclovir is administered orally.

  Oral bioavailability is around 54%

- Valaciclovir is rapidly and almost completely converted into acyclovir in the liver by the enzyme valaciclovir hydrolase.

*Distribution*

- Protein binding is low at around 10 - 30 %.
- Valaciclovir can cross the human placenta.
- Valaciclovir is excreted into breast milk in small amounts only.

*Metabolism and excretion:*

- Valaciclovir is eliminated principally as aciclovir

  Approximately 60% of a dose of acyclovir is excreted by the kidney by glomerular filtration and tubular excretion.

  9-carboxy-methoxy-methyl-guanine is the major metabolite of acyclovir.

- Half-life is around 3 hours

## Indications

Valaciclovir in indicated for:

1. Herpes simplex viruses (HSV types 1 and 2)
2. Varicella zoster virus (VZV).
   - Chickenpox
   - Treatment is indicated for treatment of herpes zoster infection in immunocompetent patients **within 72 hours** of the onset of rash. **Greatest** benefit occurs if the drug is started within **48 hours.**

     **However if there is serious disease, such as ocular involvement, or if the patient has immunocompromise then treatment should still be commenced ever after 72 hours of the onset of the rash.**
3. Prevention of CMV disease following organ transplantation
   - Treatment and prevention of CMV disease is with valganciclovir or ganciclovir).

**Note that, as for all antivirals, the prevalence of viral resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.**

## Contra-indications / precautions

The contraindications and precautions of valaciclovir are essentially those of acyclovir, and so may include:

These include:

1. Neurological abnormalities and/ or elderly:

    - Increased risk of CNS toxicity, e.g. seizures, hallucinations with IV acyclovir.

2. Renal impairment:

    - Increased risk of nephrotoxicity and neurological adverse effects; dose adjustment is required.

3. Dehydration:

    - Acyclovir crystals may precipitate in renal tubules and impair renal function.

4. Hypersensitivity to acyclovir or valaciclovir

### *Pregnancy*

Valaciclovir is a Category B3 drug with respect to pregnancy.

Category B3 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Valaciclovir is a pro-drug that is rapidly and almost completely converted to aciclovir in the body. From the limited information available, maternal use of valaciclovir has not been associated with an increased risk of major congenital malformations or adverse pregnancy outcomes.

However, as there is very limited safety information available on the use of valaciclovir during pregnancy, **aciclovir** is the preferred antiviral medicine .

### *Breast feeding*

Valaciclovir is a pro-drug that is rapidly and almost completely converted to aciclovir in the body. Small amounts of aciclovir are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant.

Therefore, valaciclovir is considered safe to use during breastfeeding.

## Adverse Effects

The adverse reactions of valaciclovir are essentially those of acyclovir, and so may include:

These may include:

1. GIT upset:
    - Nausea, vomiting, diarrhoea.
2. Renal impairment:

    Risk factors include:
    - Patients who are dehydrated
    - Excessively rapid infusion rates
    - Concomitant use of other nephrotoxic drugs
    - Pre-existing renal disease
3. Neurotoxicity (uncommon):

    Mainly seen in elderly, or those with pre-existing neurological conditions:
    - Agitation, seizures, confusion, hallucinations, altered conscious state.
4. Allergic reactions (uncommon)
5. Skin reactions:
    - Potentially serious reactions can occur, such as Stevens-Johnson syndrome and TEN.
6. TTP/HUS:
    - This has resulted in death, it has occurred in immunocompromised patients receiving acyclovir therapy.

## Dosing

*Cold sores:*

Oral, 2 grams every 12 hours for 2 doses in selected patients, e.g. with severe infection.

HIV-positive, oral 1 gram twice daily for 5 - 10 days.

Prevention, immunocompromised, oral 500 mg twice daily.

*Herpes Zoster:*

For shingles, start treatment as soon as possible and within 72 hours of rash onset.

Consider treatment after 72 hours if high risk of severe shingles or complications, e.g. ocular disease, immunosuppression, progressive clinical state

Usual adult dosing in uncomplicated herpes zoster cases is

- Oral, 1 gram 3 times daily for 7 days.

*Genital herpes:*

Initial infection, oral 500 mg twice daily for 5 - 10 days.

Recurrent infection, oral 500 mg twice daily for 3 days.

*Prevention of CMV disease:*

Oral, 2 grams 4 times daily for 90 days.

*Gertrude B. Elion (1918-1999) c. 1938 - Joint winner of the 1988 Nobel Prize in Physiology or Medicine*

*.....I had fallen in love with a young man...and we were planning to get married. And then he died of subacute bacterial endocarditis... Two years later with the advent of penicillin, he would have been saved. It reinforced in my mind the importance of scientific discovery.....*

*I had no specific bent toward science until my grandfather died of stomach cancer. I decided that nobody should suffer that much.....*

*I hadn't been aware that there were doors closed to me until I started knocking on them. I went to an all-girls school. There were 75 chemistry majors in that class, but most were going to teach it ... When I got out and they didn't want women in the laboratory, it was a shock ... It was the Depression and nobody was getting jobs. But I had taken that to*

*mean nobody was getting jobs … when I heard "You're qualified. But we've never had a woman in the laboratory before, and we think you'd be a distracting influence!.....Maybe I was young and "cute" (after all, I was only twenty then), but I've learned over the years that when you put white lab coats on chemists, they all look alike!*

*On mentoring a medical student:*
*I think it's a very valuable thing for a doctor to learn how to do research, to learn how to approach research, something there isn't time to teach them in medical school. They don't really learn how to approach a problem, and yet diagnosis is a problem; and I think that year spent in research is extremely valuable to them.*

*People ask me whether the Nobel Prize was the thing you were aiming for all your life, and I say that would be crazy. Nobody would aim for a Nobel Prize because, if you didn't get it, your whole life would be wasted. What we were aiming at was getting people well, and the satisfaction of that is much greater than any prize you can get.*

*The Nobel Prize is fine, but the drugs I've developed are rewards in themselves.*

*Gertrude B. Elion*

*References*


1. eTG - June 2019 .

2. Valaciclovir in Australian Medicines Handbook Website, Accessed June 2019

3. Valaciclovir in MIMs Website, 1 December 2014.

4. Valaciclovir in RWH Pregnancy and Breastfeeding Guidelines, 12 March 2019.



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