

VALGANCICLOVIR



*“The Human Condition” oil on canvas, 1933, René Magritte, Museum of Modern Art, New York City.*

*In scientific terms dimensions describe the minimum amount of information needed to describe the exact position of an object. In the Universe we perceive with our limited senses, four dimensions of space and time which are readily comprehensible. If super-string theory is correct however, there must exist, at some level at least, a further six dimensions of which we are completely unaware! Some high-end mathematical models have even predicted the existence of up to 22 dimensions!*

*We may describe the first four dimensions and theorize the next seven as follows:*

#### **The First Dimension:**

*A one dimensional object can be described by a single measurement, a single point on a line. This need not necessarily be limited to straight lines however. It may also for example describe a position on the circumference of a circle or a point of azimuth in the night sky*

#### **The Second Dimension:**

*A two dimensional object can be described by two separate measurements. The simplest and most intuitive example is a flat square in which any position can be defined in terms of two grid coordinates,  $x$  and  $y$  that are at right angles to each other. Two dimensional worlds, may however also exist on the surface of a cylinder or sphere.*

#### **The Third Dimension:**

*This describes the space we perceive in everyday life. The simplest and most intuitive example here is a cube. The position of any object within it can be defined in terms of three grid positions,  $x$ ,  $y$ , and  $z$ , that describe width, height and depth.*

#### **The Fourth Dimension:**

*Time represents the fourth dimension. We can not only describe the position of an object in terms of three spacial dimensions, but also the time in which the object appears at this point. This is the familiar space-time in which we perceive our Universe. The relationships between time and space are described by Einstein's theories of Relativity. As far as we know movement of time occurs along a single direction only - time's so called "arrow". We cannot revisit the past, and yet events that happen there influence our present. Because the speed of light through space (not necessarily outside of it though - as per the inflationary phase of the early Universe) has a limit, we can however, see vast distances into the past through our most powerful telescopes, though we cannot ever visit this past.*

#### **The Fifth Dimension:**

*The fifth dimension is theoretically described by the tesseract or hypercube. In geometric terms it can be described as a fourth dimension of space. We can imagine a mysterious object that has a bewildering variety of shapes, depending exactly on how it is orientated. Some theories describe quarks as having this kind of property.*

### The Sixth Dimension:

*If super-string theory is correct, then high - end mathematical models say that there are at least **six higher** dimensions within which they can “oscillate”. These dimensions are thought to only exist on a sub-atomic level within the realm of the super-strings. They are tied up into a theoretical knot-like space known as a Calabi-Yau manifold. If true then there may be alternate Universes, all born of the same conditions but with super-strings vibrating in different ways. Mastery of both the fifth and sixth dimensions, could enable time travel.*

### The Seventh Dimension:

*The seventh dimension is theoretically similar to the sixth, however, alternate Universes, instead of all being born out of similar conditions, are born out of different unique conditions. Instead of alternate realities within similar Universes, the Universes themselves are completely different. Some could support life as we know it, but most would not.*

### The Eighth Dimension:

*The eighth dimension is a theoretical extension of the seventh. Here any given Universe, rather than following its fixed predetermined course of evolution, itself branches out endlessly into new alternate realities. In other words the timeline of a particular Universe is not fixed on one course by its initial conditions, rather it can branch and evolve - ad infinitum!*

### The Ninth Dimension:

*In the seventh dimension Universes are born out of differing initial conditions, however, these conditions are still all described by the **same** fundamental laws of nature. In the ninth dimension Universes are born and exist according to variable laws of nature. Unimaginably bizarre Universes of which we may barely be able to conceive, may exist.*

### The Tenth Dimension:

*Beyond the ten dimension we truly reach the realm of “metaphysics”. The tenth dimension is one in which Universes exist that are (barely) within the capability of humans to comprehend.*

### The Eleventh Dimension:

*The eleventh dimension, by extension of the tenth, are Universes that exist, that are beyond the human mind, in its current state of evolution, to comprehend on any level at all.*

**TIME TRAVELLER:**  
***New Year’s eve, 1899***

*I wanted to finish the job before the new century began. - I barely made it.*

**BRIDEWELL:** *Marvelous.*

**DR. HILLYER:** *(Stands up) What is it?*

**TIME TRAVELLER:** *Well, it has to do with time.*

**DR. HILLYER:** *(Steps to box) I've always maintained what this nation needs is a reliable timepiece. The Navy needs one. The Army needs one. - For the artillery you know.*

**KEMP:** *(Leaning forward) Couldn't do better, George. So that's why you've been in hiding. Clever of you, indeed!*

**FILBY:** *(Studying the Time Traveller's reaction) I don't believe George is referring to a new kind of timepiece.*

**TIME TRAVELLER:** *When I speak of time, I'm referring to the fourth dimension.*

*A perplexed look comes over Bridewell's face. Dr. Hillyer registers concern. Kemp looks troubled. Only Filby expresses avid interest.*

**FILBY:** *Go on, George.*

**TIME TRAVELLER:** *Now, as you know, the difficulty in explaining the fourth dimension is that it cannot be seen or felt - it must be thought of.*

**FILBY:** *If you don't mind, George, would you refresh me on the first three dimensions.*

**DR. HILLYER:** *Really, Filby, they must have taught you something at school!*

**BRIDEWELL:** *(Baiting Dr. Hillyer) Suppose you explain it, Doctor.*

**DR. HILLYER:** *Certainly! (He demonstrates pompously) When I move in a straight line, forward or backward, that's one dimension. - When I move to the left or right, two dimensions - When I move up and down, three dimensions. (a bright idea lights up his face. At last he can get ahold of the box, but Filby interferes before Dr. Hillyer can get his fingers on it and he has to be satisfied with merely pointing) For instance, this box has three dimensions: length, breadth, and height.*

**BRIDEWELL:** *(Amazed) Well, then, what's the fourth dimension?*

**DR. HILLYER:** *Well, that's...that's mere theory! No one can really say what the fourth dimension is or even that it exists.*

**TIME TRAVELLER:** *Leaning forward in his chair). On the contrary, Doctor!  
The fourth dimension is as true and as real a dimension as  
any of the other three. In fact, they couldn't exist without it.*

**DR. HILLYER:** *How do you mean?*

**TIME TRAVELLER:** *Well, take that box. It has the first three dimensions, as you  
said. But what if it didn't exist in Time? It wouldn't exist at  
all, would it?*

**DR. HILLYER:** *No.*

**TIME TRAVELLER:** *So - for an object to exist at all, it must exist in the fourth  
dimension....and that fourth dimension is duration....**Time!***

**DR. HILLYER:** *(Impatiently) All right! But what's in that box?*

**TIME TRAVELLER:** *I'm coming to that. But first, consider! Why is it that we  
usually ignore the fourth dimension? Because we have no  
freedom to move in it. We can move in the other three -- up,  
down, forward, backward, sideways. But when it comes to  
Time.....we are prisoners.....*

*David Duncan, 1960 Screenplay for H.G Wells, "The Time Machine", 1894.*

*I CALL our world Flatland, not because we call it so, but to make its nature clearer to  
you, my happy readers, who are privileged to live in (three dimensional) Space. Imagine  
a vast sheet of paper on which straight Lines, Triangles, Squares, Pentagons, Hexagons,  
and other figures, instead of remaining fixed in their places, move freely about, on or in  
the surface, but without the power of rising above or sinking below it, very much like  
shadows - only hard and with luminous edges - and you will then have a pretty correct  
notion of my country and countrymen. Alas, a few years ago, I should have said "my  
universe": but now my mind has been opened to higher views of things.*

*In such a country, you will perceive at once that it is impossible that there should be  
anything of what you call a "solid" kind; but I dare say you will suppose that we could at  
least distinguish by sight the Triangles, Squares, and other figures, moving about as I  
have described them. On the contrary, we could see nothing of the kind, not at least so as  
to distinguish one figure from another. Nothing was visible, nor could be visible, to us,  
except Straight Lines; and the necessity of this I will speedily demonstrate.*

*Place a penny on the middle of one of your tables in (three dimensional) Space; and  
leaning over it, look down upon it. It will appear a circle. But now, drawing back to the  
edge of the table, gradually lower your eye (thus bringing yourself more and more into  
the condition of the inhabitants of Flatland), and you will find the penny becoming more  
and more oval to your view; and at last when you have placed your eye exactly on the  
edge of the table (so that you are, as it were, actually a Flatlander) the penny will then  
have ceased to appear oval at all, and will have become, so far as you can see, a straight  
line.*

*The same thing would happen if you were to treat in the same way a Triangle, or Square, or any other figure cut out of pasteboard. As soon as you look at it with your eye on the edge on the table, you will find that it ceases to appear to you a figure, and that it becomes in appearance a straight line. Take for example an equilateral Triangle - who represents with us a Tradesman of the respectable class. Fig. 1 represents the Tradesman as you would see him while you were bending over him from above; figs. 2 and 3 represent the Tradesman, as you would see him if your eye were close to the level, or all but on the level of the table; and if your eye were quite on the level of the table (and that is how we see him in Flatland) you would see nothing but a straight line.*

Edwin A. Abbott, "Flatland", 1884.

*Edwin A. Abbott in his 1884 classic "Flatland", imagines beings who inhabit a two dimensional world. These beings cannot imagine a three dimensional world. However the hero of the story, "A. Square" is visited by a being from the third dimension, "A. Sphere", who shows him his world. The two dimensional being is profoundly shocked. When he returns to his world he tries to convince his fellow two dimensional beings of the existence of a third dimension, but no one believes him and he is eventually imprisoned for being mentally ill and disturbing the peace! The magisterial H.G Wells, the father of all modern science fiction and its greatest exponent, a decade later developed the theme further. He imagines travel through a higher dimension than the three our senses normally perceive, a dimension in his time only very dimly perceived as the fourth - time. Just as Abbot's hero "A. Square" is unable to convince his fellow beings of the existence of a higher dimension, so Well's hero, the "time-traveller" is unable to convince his colleagues of the existence of time as the fourth dimension.*

*During the course of the Twentieth century, truly astonishing advances were made in the field of theoretical physics. Giants of the age such as Penrose, Hawking and Witten struggled to develop a theory of everything that would explain the true nature of the Universe, where Newtonian Physics, Einstein's Relativity, and Niels Bohr's disturbing Quantum Mechanics, still did not seem enough to explain all observations of Nature. In the 21st century our current best guess for a theory of everything, the giants of Physics tell us, lies perhaps within the realm of string theory, a theory described by mathematical equations that lie on the very limits of the capacity for human understanding. A profound consequence of this, and other models, is the possible existence, at some level beyond our ability to perceive, or even to conceive them, multiple higher dimensions of reality.*

*The brilliant Surrealist, René Magritte, perhaps best summed up the "Human Condition" in 1933. It is as though we perceive the world with our limited senses as a flat two dimensional canvas, a greatly impoverished mental construction of a an unimaginably richer reality that lies beyond our understanding.*

*The purine nucleoside synthetic analogue antiviral agents, play a trick upon unsuspecting susceptible viruses. These viruses inhabit a simple "flatland" of their own, unable to perceive subtle differences of a higher reality, when it comes to the nucleoside analogue antiviral agents.*

# VALGANCICLOVIR

## Introduction

**Valganciclovir** is a an **orally** active **prodrug** of **ganciclovir**, which, after oral administration, is rapidly converted to **ganciclovir** by intestinal and hepatic esterases.

**Ganciclovir** is a purine (guanine) nucleoside synthetic analogue antiviral agent which is active against herpes viruses, in general, but more particularly against **CMV**.

Its principal use is in the treatment and prevention of **CMV infections**, specifically:

1. CMV retinitis in AIDS
2. Prevention of CMV disease after solid organ transplantation in people at risk

## 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.

**Valganciclovir** was introduced into clinical practice in 1994.

## 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**.

**Valganciclovir** is a synthetic L-valyl ester salt (i.e prodrug) of ganciclovir. which, after oral administration, is rapidly converted to ganciclovir by intestinal and hepatic esterases.

It is a polar hydrophilic compound.

## 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

Valganciclovir hydrochloride as:

Tablets:

- 450 mg.

Oral liquid:

- 50 mg/mL (as powder for reconstitution), 100 mL.

## Mechanism of Action

**Valganciclovir**, after oral administration, is rapidly converted to **ganciclovir** by intestinal and hepatic esterases.

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

Ganciclovir needs to be phosphorylated to the active compound, ganciclovir triphosphate, in order to become active against the virus.

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

## Pharmacodynamics

**Ganciclovir** has activity against herpes viruses including:

1. Cytomegalovirus
2. Herpes simplex virus 1 and 2
3. Herpesvirus type 6, 7 and 8
4. Varicella zoster virus (VZV)
5. Epstein-Barr virus (EBV)

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

### Pharmacokinetics

#### Absorption:

- Valganciclovir is administered orally.

After oral administration, it is **rapidly** converted to **ganciclovir** by intestinal and hepatic esterases.

Ganciclovir concentrations following oral valganciclovir are **similar** to those from IV ganciclovir. <sup>2</sup>

#### Distribution

- Plasma protein binding of **ganciclovir** is negligible at just 1-2 %.

Therefore, drug interactions involving protein binding site displacement are not expected.

- Valganciclovir (as well as ganciclovir) can cross the human placenta.
- It is unknown if valganciclovir or ganciclovir is excreted into human breast milk.

#### Metabolism and excretion:

- **Ganciclovir** is excreted unchanged by the kidneys, via both glomerular filtration and active tubular secretion.
- Clearance of **ganciclovir** is progressively reduced with increasing degrees of renal impairment.

### Indications

Specific **CMV related** indications include:

1. CMV retinitis in AIDS
2. Prevention of CMV disease after solid organ transplantation in people at risk

*In general terms, indications for the guanine analogue drugs are:*

1. Treatment and prevention of **herpes simplex** infections (aciclovir, famciclovir, valaciclovir)
2. **Shingles** (aciclovir, famciclovir, valaciclovir)
3. Treatment and prevention of **CMV** disease (ganciclovir, valganciclovir)

### Contra-indications / precautions

These include:

1. Allergy to valganciclovir (or ganciclovir, its active metabolite)
2. Patients with bone marrow suppression: <sup>2</sup>

Patients with bone marrow suppression may be more susceptible to the myelosuppressive effects of ganciclovir; dosage adjustment and/or blood examination each week (or more frequently) may be required.

Avoid use, particularly if:

- Neutrophil count is  $< 0.5 \times 10^9$  cells/L
  - Platelet count is  $< 25 \times 10^9$ /L
  - Haemoglobin is  $< 80$  g/L.
3. Contraception: <sup>2</sup>
    - Women should use effective contraception while taking ganciclovir.
    - Manufacturer recommends that men use barrier contraception during, and for at least 90 days after, treatment with ganciclovir.
  4. Drug Interactions:
    - Concurrent treatment with **imipenem - cilastatin** may increase the risk of seizures - this combination should be avoided.
  5. Renal impairment:
    - Dosage adjustment is required if the CrCl is  $< 60$  mL/minute.

6. Pregnancy - contraindicated (see below)
7. Breast feeding - contraindicated (see below)

### Pregnancy

Valganciclovir is a **category D** drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Valganciclovir is contraindicated in pregnancy as its active metabolite, **ganciclovir**, is teratogenic and embryotoxic in animals.<sup>2</sup>

Published reports describing the use of valganciclovir during pregnancy have not been located. Valganciclovir is a pro-drug that is rapidly converted to ganciclovir in the body .

Case reports of ganciclovir use during pregnancy have not described congenital malformations or adverse pregnancy outcomes.

If valganciclovir is required during pregnancy, consultation with an Infectious Diseases specialist or Clinical Microbiologist for further advice is recommended.

Follow-up and monitoring of both maternal and fetal wellbeing by a multidisciplinary team is also recommended.

The manufacturer recommends women receiving valganciclovir treatment should use effective contraception during, and for 30 days after stopping therapy.

### Breast feeding

Published reports describing the use of valganciclovir during breastfeeding have not been located.

Valganciclovir is a pro-drug that is rapidly converted to ganciclovir in the body.

Due to potential serious adverse effects in the breastfed infant, consider an alternative medicine during breastfeeding or avoid breastfeeding while undergoing valganciclovir treatment.

### Adverse Effects

As **ganciclovir** is the active metabolite of valganciclovir, the adverse effects of valganciclovir are essentially those of ganciclovir.

The principal adverse effects of ganciclovir include:

1. GIT upset:
  - Nausea, vomiting, diarrhoea, abdominal pain.
2. Blood dyscracias:

Reactions are generally dose dependant.

They can be severe and may include:

- Anaemia
- Neutropenia
  - ♥ Neutropenia is dose-dependent and reversible; usually occurs during the first 1 - 2 weeks of treatment
- Thrombocytopenia

Ganciclovir should, therefore, be used with caution in patients with pre-existing cytopenias, or who have received or are receiving myelosuppressive drugs or radiation therapies.

Cell counts usually begin to recover within 3 -7 days of cessation of treatment.

3. Neurological effects:
  - Sedation, ataxia, confusion, convulsions.

### Dosing

**Exact dosing and duration of dosing must be individualized and guided by specialists experienced in the treatment of CMV infections.**

In **general** terms, usual dosing in adults is as follows: <sup>2</sup>

#### CMV retinitis:

Induction, oral 900 mg twice daily for 14 - 21 days.

Maintenance, oral 900 mg once daily.

#### Prevention of CMV disease after transplant: <sup>2</sup>

Oral, up to 900 mg once daily, beginning within 10 days of the transplant and continuing for at least 100 days, depending on the organ and local protocol.

Oral, dose (mg) = 7 x BSA x CrCl once daily, up to a maximum of 900 mg once daily.

Body surface area (BSA) and CrCl are calculated using the equations below.

Use  $\text{CrCl} = 150 \text{ mL/minute}/1.73 \text{ m}^2$  if the calculated CrCl exceeds this value.

The CrCl equation above is revised from the original Schwartz equation used in the product information. It may not provide an accurate estimate of CrCl at higher levels of renal function and has not been validated in children aged <1 year. Seek specialist advice for these patients.

Monitoring:

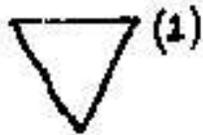
Measure complete blood count 2 or 3 times each week at induction, then each week during maintenance treatment

Monitor electrolytes and renal function 2 or 3 times each week

Measure liver enzymes before starting treatment, then each month



*The Time Traveller (Australian actor, Rod Taylor, second from left) with his companions, new year's eve, 1899. (H.G Wells, "The Time Machine", Galaxy films, 1960).*



*.....Take for example an equilateral Triangle - who represents with us a Tradesman of the respectable class. Fig. 1 represents the Tradesman as you would see him while you were bending over him from above; figs. 2 and 3 represent the Tradesman, as you would see him if your eye were close to the level, or all but on the level of the table; and if your eye were quite on the level of the table (and that is how we see him in Flatland) you would see nothing but a straight line.....*

*Edwin A. Abbott, "Flatland", 1884.*

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2. Valganciclovir in Australian Medicines Handbook Website, January 2019.
3. Valganciclovir in MIMs Website, 1 November 2015.
4. Valganciclovir in RWH Pregnancy and Breast feeding Guidelines, 12 March 2019.

### Further reading:

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H.G Wells, "The Time Machine", 1894.

Edwin A. Abbott, "Flatland", 1884.

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