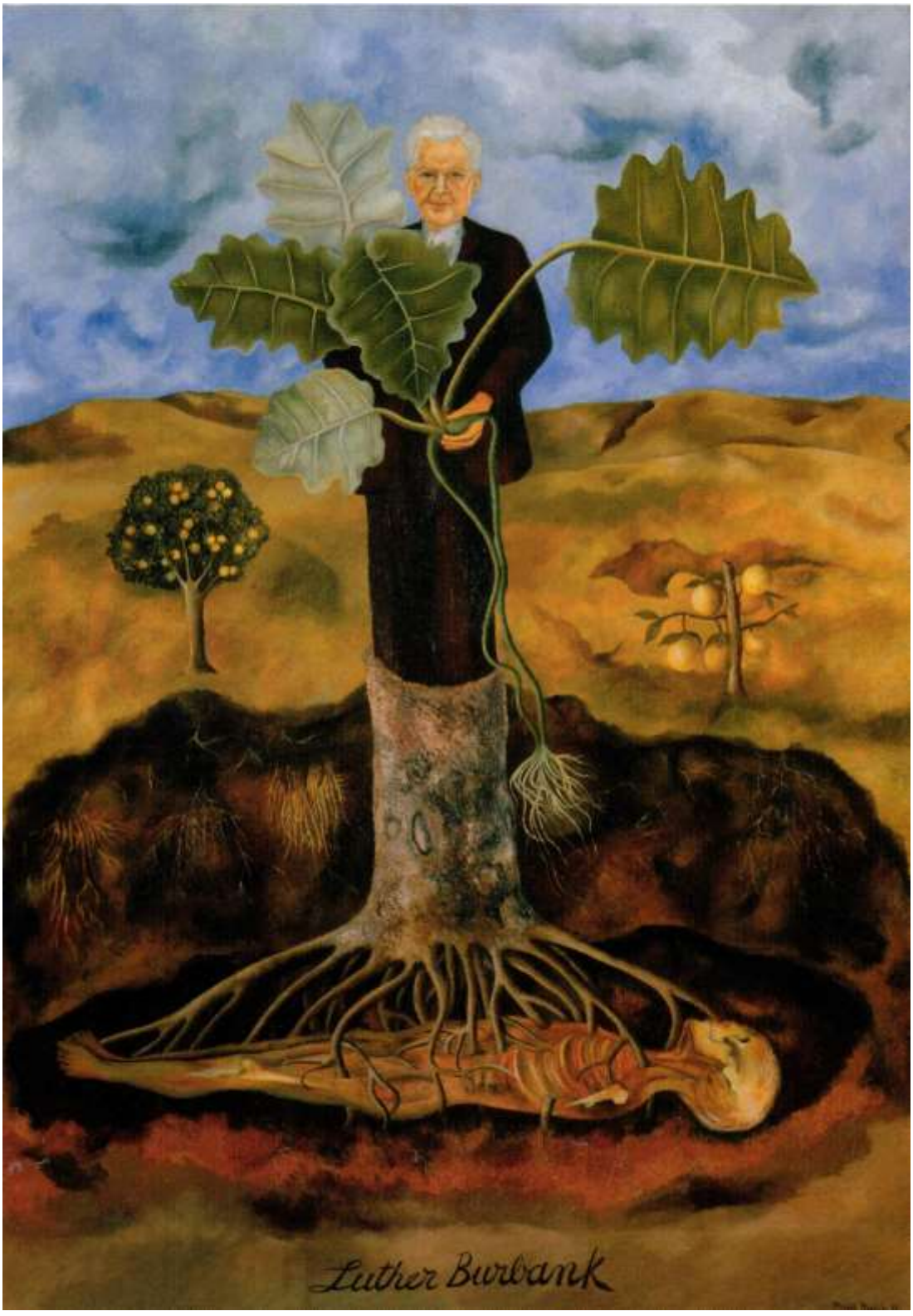
THE NORTHERN HOSPITAL

VORICONAZOLE



"Portrait of Luther Burbank", oil on masonite, 1931, Frida Kahlo

"My surprise and joy were unbounded when I discovered on my arrival in Mexico, that her work had blossomed forth, in her latest paintings, into pure surreality, despite that it had been conceived without my prior knowledge whatsoever of the ideas motivating the activities of my friends and myself. Yet at this present point in the development of Mexican painting, which since the beginning of the nineteenth century has remained largely free from foreign influence and profoundly attached to its own resources, I was witnessing here, at the other end of the earth, a spontaneous outpouring of our own questioning spirit: what irrational laws do we obey, what subjective signals allow us to establish the right direction of any moment, which symbols and myths predominate in a particular conjunction of objects or web of happenings, what meaning can be ascribed to the eye's capacity to pass from visual power to visionary power?

This art even contains that drop of cruelty and humour uniquely capable of blending the rare effective powers that compound together to form the philtre which is Mexico's secret. The power of inspiration here is nourished by the strange ecstasies of puberty and the mysteries of generation, and, far from considering these to be the mind's private preserves, as in some colder climates, she displays them proudly with a mixture of candour and insolence....."

Andre Breton, brochure for Frida Kahlo's first solo exhibition,
Julien Levy Gallery New York, 1938.

"I never knew I was a Surrealist, until Andre Breton came to Mexico and told me I was one....I myself still don't know what I am....."

Frida Kahlo, 1938.

"You have no idea the kind of bitches these people are. They make me vomit. They are so damn "intellectual" and rotten that I can't stand them anymore. It is really too much for my character. I rather sit on the floor in the market of Toluca and sell tortillas, than to have anything to do with those "artistic" bitches of Paris. They sit for hours on the "cafes" warming their precious behinds, and talk without about "culture" "art" "revolution", and so on and so forth, thinking themselves the gods of the world, dreaming the most fantastic nonsenses, and poisoning the air with theories and theories that never come true. Next morning - they don't have anything to eat in their houses because none of them work and they live as parasites of the bunch of rich bitches who admire their "genius" of "artists" Shit and only shit is what they are. I never seen Diego or you Muray, wasting their time on stupid gossip and "intellectual" discussions - Gee weez! It was worthwhile to come here only to see why Europe is rottening, why all this people - good for nothing - are the cause of the all the Hitlers and Mussolinis. I bet you my life I will hate this place and its people as long as I live. There is something so false and unreal about them that they drive me nuts...."

Frida Kahlo, Paris, 1939.

The self proclaimed "Pope" of Surrealism of the mid-Twentieth century, Frenchman Andre Breton, was astonished by the work of Frida Kahlo, when he first came across it. He immediately considered her a "self-made" Surrealist, who despite, "living at the other end of the Earth", had somehow managed to become by some miracle of

convergent evolution a true Surrealist. Breton, needless to say, considered Surrealism to be the highest form of Art and culture and so - quite condescendingly - was amazed that Surrealism had established itself independently outside of Paris!

Breton simply could not conceive of the possibility that a different Art form could express the true subconscious. He had set himself up as the spokesperson for the genre, wrote its manifesto, and then pompously proceeded to dictate to other Surrealists, what was and what was not Surrealist Art, earning the ill will of the maestro Surrealist himself, Salvador Dali. He let Frida know, in no uncertain terms, what she was. "I never knew I was a "Surrealist" Frida quipped, "until Andre Breton came to Mexico and told me I was one!" While it was true that Frida probably came into contact with the Surrealism when she was in San Francisco in 1931 and that it can be argued that some aspects of her style at least could be described as Surrealist, she herself always denied she was one. Like Edgar Degas who always insisted that he was a "Realist" and not an "Impressionist", Frida similarly insisted she was a "Realist", a point of view that was strongly supported by her famous husband, the great Mexican Muralist, Diego Rivera.

What Frida painted was not some nonsensical or utterly incomprehensible deeply hidden subconscious emotion, rather she painted reality, usually her own, and in her own rich language of symbolic motifs. Though her works do have something of the Surrealist style about them, just as Degas certainly had those of Impressionism about his, this is only a superficial observation. Surrealism, like Impressionism in the Nineteenth century, was more than simply an Artistic style, it was a whole philosophy of life. It was in this sense that Degas denied he was an Impressionist and it was also in this sense that Frida denied she was a Surrealist. "I don't paint dreams or nightmares" she explained, "I paint my own reality".

Frida's earliest works were modeled after the Renaissance, Mannerism, and modern European styles, but after her marriage to Diego Rivera, attracted in part by his own interests, she quickly developed a deep love of her own native Mexican heritage and culture. Her works are deeply personal and richly embroidered with recurring Catholic, (despite being an ardent Communist) and pre-Columbian symbolism. In truth Frida's work is simply not classifiable into any Twentieth century genre - her style is strikingly unique - an alloy of her own deeply personal emotions strikingly expressed in the language of her native Mexican heritage. Frida's magisterial biographer, Hayden Herrera has explained this best; "Mexico had its own magic and myths, and thus did not need foreign notions of fantasy. The self-conscious search for subconscious truths that may have provided European Surrealists with some release from the confines of the rational world and ordinary bourgeois life offered little enchantment in a country where reality and dreams are perceived to merge and miracles are thought to be daily occurrences".

While some Surrealist works can be explained or at least interpreted in logical ways, depending on the actual Artist, much of it is simply unintelligible to anyone but the Artist who produced it. The earliest work of Frida's where we see the evolution from a traditional European style to a "Surrealist style", is the fascinating work, "Portrait of Luther Burbank", oil on masonite, 1931, produced in the year when she lived in San Francisco. At first glance it's a disturbingly creepy image. But understanding and recognizing Frida's symbolic language, it is transformed into a heartfelt tribute to a

brilliant horticulturist and is a celebration of life. Burbank, died in 1926, and was buried under his favourite cedar of Lebanon tree at his California home, a tree he had grown and nurtured from a seed. He was famed for his ability to create new plant and vegetable hybrids, including the Russet-Burbank potato which would become the world's predominant potato in food processing. He wanted no marker for his grave, preferring instead, the idea of a living memorial, one that he had cherished in life. Frida and Diego had met Burbank's widow. She explained to Frida that her husband had told her, "I would like to know that the strength of my body is going into the strength of my tree". Frida wrote to her mother, on the back of a photo of the her and Diego beside the tree, "Dearest mamacita, here we are in front of the tree where Luther Burbank is buried. He was a wise man from here, who grew fruits and flowers through thousands of grafts to produce even more wonderful ones". Burbank made quite an impression on both Diego and Frida. Diego depicted him in his mural "Allegory of California".

In Frida's portrait Burbank is depicted as a hybrid himself. His body has gone to dust in the grave, but from death comes new life, which was one of Frida's strongest motifs. Burbank lives again in his beloved tree. There is the undoubted Catholic symbolism of resurrection, but Frida was not religious. Her symbolism is a more deeply universal one - derived of the ancient "atomism" philosophy of Epicurus and his great Roman disciple, Lucretius. The Epicureans believed in the universal connectedness of every object alive or inanimate through the eternal recycling of immortal atoms - a philosophy so heretical that following the fall of the Western Roman Empire, the Catholic Church suppressed it for close on one and half millennia, till the time of Dalton, Thomson and Rutherford.

The image of a decaying corpse displayed in a portrait, dedicated to a great man, may seem macabre to many. It is as if the rotting body has become consumed by some horrible fungal mycelium, and Burbank himself now rises like some gargantuan fruiting mushroom above the ground. But all this is to misunderstand Mexican tradition and culture. Mexicans embrace death as a normal part of life and rather than fear it, in their typically "machismo" fashion, they defy it, even make fun it in their great "Festival of the Dead" - a time when friends and family get together to remember their deceased ancestors and loved ones. But there is no sadness, rather it is total celebration in the form of a Halloween on steroids!

While it is true that all life is interconnected, sadly things are not always as Epicureanly idyllic as Mexican tradition may have it. Although many species of fungi live with us harmoniously and most helpfully, there are others that may wage war upon us. Though these organisms, have every right to exist in an Epicurean Universe, we may be forced from time to time to accelerate their cycle through life by use of potent antifungal drugs of mass destruction!

VORICONAZOLE

Introduction

Voriconazole, (trade name in Australia "**Vfend"**) is a second-generation, extended spectrum **triazole antifungal agent** used to treat and prevent serious invasive fungal infections.

It is available in both oral and IV formulations.

It is effective in particular for **aspergillosis** and **candida** infections.

It is **not** effective for the potentially life-threatening **mucormycete** fungi.

History

The development of antifungal drugs was much slower than that of the antibacterials. The main reason for this was that fungi are a eukaryotic species which are biochemically more similar to human hosts as compared to the prokaryotic bacteria. Developing a drug to combat fungal infections whilst not harming the human host therefore was a very much more difficult task.

Nystatin was the first **polyene** antifungal agent to be introduced into clinical practice in 1949. Amphotericin B was developed later and became the mainstay of therapy for serious fungal infections, even though it was relatively toxic, as there was no better alternative agent.

The search for new and less toxic antifungals led to the discovery of the azoles several decades later. Ketoconazole, an imidazole was the first compound that could be used for the oral treatment of systemic fungal infections. It was introduced in the early 1980s.

The development of the first-generation triazoles represented a second major advance in the treatment of fungal infections. Both fluconazole and itraconazole displayed a broader spectrum of antifungal activity than the imidazoles and had a markedly improved safety profile compared with amphotericin B and ketoconazole. The so-called "second-generation" triazoles, were then developed that had greater potency and increased activity against resistant and emerging pathogens, in particular against the Aspergillus species.

Chemistry

Voriconazole is an triazole azole derivative.

Biology

A **fungus** is any member of the group of eukaryotic organisms that includes:

1. Yeasts:

    - Yeasts are *microscopic* eukaryotic, **single-celled** microorganisms

Candida albicans is an opportunistic pathogenic yeast

2. Molds:

- Molds are *microscopic* **multicellular** organisms typically arranged into filaments called hyphae

3. Mushrooms:

- A mushroom, (or toadstool), is the *macroscopic* fleshy, spore-bearing fruiting body of a fungus, typically produced above ground on soil or on its food source.

Classification

The five classes of antifungal agents are:

1. Polyenes:

These include:

- Amphotericin B
- Nystatin

2. Azoles:

Azole antifungal drugs (except for abafungin) inhibit the fungal cytochrome P450 enzyme lanosterol 14 α-demethylase. This enzyme is necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth

- Imidazoles

  These include:

  - ♥ Clotrimazole
  - ♥ Econazole
  - ♥ Ketoconazole
  - ♥ Miconazole

- Triazoles:

  Systemic agents include:

First generation agents:

- ♥ Fluconazole
- ♥ Itraconazole

Second generation (extended spectrum) agents:

- ♥ **Voriconazole**
- ♥ Posaconazole

- Thiazoles
  - ♥ Abafungin

3. Allylamines:

These include:

- Amorolfin
- Butenafine
- Naftifine
- Terbinafine

4. Echinocandins:

These include:

- Anidulafungin
- Caspofungin
- Micafungin

5. Others:

These include:

- Griseofulvin
- Flucytosine
- Pentamidine (effective against Pneumocystis jirovecii (previously P. carinii).

Preparations

Voriconazole as:

Tablets:

- 50 mg
- 200 mg.

Oral liquid:

- 40 mg/mL (as powder for reconstitution in 70 ml water)

  Oral liquid is equivalent to tablets in healthy adults. [2]

Vials, (powder for IV reconstitution):

- 200 mg

Mechanism of Action

The azoles as a class are generally **fungistatic** agents.

Azoles impair the synthesis of **ergosterol** in **fungal cell membranes** leading to their breakdown.

Cell leakage and death then occur by lytic activity of the host defense system.

Pharmacodynamics

Voriconazole is a relatively broad-spectrum anti-fungal agent, effective in the treatment of:

1. Invasive aspergillosis
2. Serious Candida infections:
   - Including fluconazole resistant C. krusei and resistant strains of C. glabrata and C. albicans.
3. Other serious infections caused by:
   - Scedosporium (S. prolificans is less susceptible)
   - Fusarium spp.

Pharmacokinetics

Absorption:

- Voriconazole can be administered orally or IV
- It is rapidly and almost completely absorbed following oral administration.

  Oral bioavailability is high in adults at around 96 %, but is somewhat less than this in children.

  Maximum plasma concentrations are achieved 1 - 2 hours after dosing.

Distribution

- The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues.
- Protein binding is only moderate at around 58%
- Voriconazole is thought likely to cross the human placenta.
- Voriconazole is thought likely to be distributed into human breast milk.

Metabolism and excretion:

- Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.

  It is metabolized by the hepatic cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4.

  CYP2C19 is **significantly** involved in the metabolism of voriconazole and this enzyme exhibits genetic polymorphism.

  Voriconazole concentrations can be highly variable, partly because of differences in the **CYP2C19** genotype that result in slow and fast metabolizers of the drug.

- The major metabolite of voriconazole is the N-oxide, which accounts for around 70% of the metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.
- Elimination half-life is around 6 hours.

Indications

Indications include:

1. Invasive aspergillosis

2. Serious Candida infections, including C. krusei

3. Other serious infections caused by:

   - Scedosporium (S. prolificans is less susceptible)
   - Fusarium spp.

4. Prevention of invasive fungal infections in people at risk:

   - e.g. haemopoietic stem cell recipients (seek specialist advice)

Contra-indications/precautions

These include:

1. Known hypersensitivity to voriconazole.

2. Risk factors for prolonged QT interval

   - Voriconazole may prolong the QT interval and so increase the risk of arrhythmia.

     Combinations with drugs that also prolong the QT interval should be used cautiously; the manufacturer contraindicates combinations with drugs metabolized by CYP3A4 and which also prolong the QT interval.

3. Risk factors for skin cancer:

   - e.g. immunosuppression - voriconazole increases the risk of developing skin cancer.

4. Drug interactions:

   - There are *many* potential drug interactions with voriconazole

     Compatibility should be checked

     A useful resource in this regard is the Australian Medicines Handbook Website

Pregnancy

Voriconazole is classified as 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.

There is very limited information available describing the use of voriconazole during pregnancy.

There has been one case report describing maternal use of voriconazole with no adverse effects observed in the newborn .

Therefore, due to the limited information available, consider an alternative medicine during pregnancy.

Consultation with an Infectious Diseases specialist or Clinical Microbiologist for further advice is also recommended.

Breast feeding

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

Voriconazole is likely to be excreted into breast milk, as the medicine has a low molecular weight and is poorly bound to plasma proteins.

Therefore, due to a lack of safety information and potential adverse effects in breastfed infants, consider an alternative medicine during breastfeeding if possible.

Adverse Effects

These include:

1. Anaphylactoid reactions:

    - These may occur at the start of infusion.

      Features include fever, flushing, sweating, dyspnoea, nausea, itch and rash.

      Consider slowing or stopping voriconazole if they are severe.

2. Local injection site reactions

3. GIT upset:

    - Nausea, vomiting, abdominal pain, diarrhoea

4. Visual disturbances:

- About 30% of people in clinical trials had altered visual perception, such as blurred vision, colour changes or photophobia within 30 minutes of dosing.

  These reactions are dose-related, reversible and generally resolve within an hour.

  However, healthy volunteers taking voriconazole for 28 days had retinal abnormalities during this period, which returned to normal 14 days after stopping.

  Some long-term follow-up data indicate that there is no residual effect on vision or the retina; however, optic neuritis has been reported.

5. Dermatological reactions:

   These include:

   - Urticaria
   - Serious hyper sensitivity reactions:
     - ♥ Stevens-Johnson syndrome / toxic epidermal necrolysis
   - Photosensitivity reactions:

     These are more common in children.

     - ♥ Exposure to sunlight during **long-term** treatment may be associated with melanoma and squamous cell carcinoma (usually in the **immunosuppressed**), and accelerated photoageing (e.g. lentigines, actinic keratoses). Squamous cell carcinoma has been seen in children and adults and may be aggressive.

6. Prolonged QT interval

7. Hepatic impairment:

   - Abnormal liver function tests appear to be dose-related.

     Serious hepatotoxicity including hepatic failure can rarely occur.

8. Blood dyscrasias:

   - Anaemia
   - Thrombocytopenia

9. Alopecia:

- Usually with prolonged courses

10. Proliferation of resistant species:

    - Infection with voriconazole-resistant moulds or yeasts, such as the **mucormycete fungi**, may occur during treatment or prophylaxis with voriconazole.

Dosing

In general terms, usual adult and child >14 years, dosing is:

IV:

Loading dose:

- IV, 6 mg/kg every 12 hours for 2 doses.

Maintenance:

- IV, 3 - 4 mg/kg every 12 hours.

Dilute to concentration of 0.5 - 5 mg/mL in sodium chloride 0.9% or glucose 5% and infuse over **1 - 2 hours** at no more than **3 mg / kg / hour.** [2]

Oral:

Oral, > 40 kg:

- 400 mg every 12 hours for 2 doses.

Oral, < 40 kg:

- 200 mg every 12 hours for 2 doses.

Hepatic impairment:

Halve the maintenance dose in mild-to-moderate hepatic cirrhosis.

See latest Therapeutic Guidelines for full prescribing details.

Monitoring:

IV therapy:

Many factors influence the plasma concentration of voriconazole and so monitoring levels is generally recommended in those whom prophylaxis or treatment is likely to be used for more than a few days.

Voriconazole concentrations are highly variable, partly because of differences in CYP2C19 genotype that result in slow and fast metabolizers of the drug.

A trough concentration between 1 mg/L - 5 mg/L is commonly recommended for clinical efficacy. [1]

Plasma concentrations outside the therapeutic range may be more common in: [1]

- Children
- Underweight or obese patients
- Patients with hepatic impairment
- Genetic polymorphisms
- Clinically significant drug interactions.

Oral therapy:

Check renal and hepatic function at baseline and regularly during treatment (more frequently if abnormalities develop)

Clinical:

Monitor **visual function** if treating for > 28 days.

Monitor for **skin damage** and **skin cancers** during long term treatment (consider stopping treatment if chronic phototoxicity occurs); long-term dermatological follow-up may be necessary, e.g. in children, if phototoxic reactions occur as squamous cell carcinoma may result.

Frida Kahlo and Diego at Luther Burbank's Garden, Santa Rosa, 1931

References

1. eTG - July 2019.

2. Voriconazole, in Australian Medicines Handbook Website, January 2019

3. Voriconazole, in MIMs Website, 1 July 2019.

4. Voriconazole, in RWH Pregnancy & Breastfeeding Guidelines; 12 March 2019.

Dr J. Hayes
Reviewed 1 July 2019