

Ivermectin in the treatment of COVID-19— friend or foe?

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The global number of deaths due to COVID-19 is almost at the two million mark, with over 35 000 deaths in South Africa. Although there are hopes of a safe and effective vaccination programme, the increasing number of COVID-19 cases in the country is putting a significant strain on the healthcare system. Ivermectin, an antiparasitic drug, has been widely published on social media platforms and news outlets as a so-called miracle drug for the treatment of COVID-19. Ivermectin is not registered in SA as a drug for human use, but rather as a veterinary and agricultural product. Currently, from a small number of randomised controlled trials (RCTs), there does seem to be a signal of evidence for the use of ivermectin in the management of COVID-19. Pharmacists must, however, remain cognisant of their ethical responsibilities as well as the applicable regulations that prohibit the procurement and dispensing of any unregistered medicine.

Keywords: COVID-19, SARS-CoV-2, ivermectin, avermectin, macrocyclic lactone, endectocide

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Introduction

Nearly one year ago, the first death from COVID-19 was reported and globally there have been almost two million deaths from the COVID-19 virus to date.¹ In South Africa, 1 278 303 have been diagnosed with the COVID-19 virus, with 35 140 deaths being documented.² While the roll-out of a safe and effective vaccination programme is being eagerly anticipated, the rise in the number of newly-diagnosed COVID-19 cases, as well as the increase in the associated number of deaths, presents an unprecedented challenge to the already strained healthcare system in the country.

In the late 1970s, ivermectin was developed as a compound belonging to a new class of drugs in the treatment of both ecto- and endo-parasitic infections.³ Initially used in veterinary medicine, it was soon found to be safe and effective in humans as well.³ It has successfully been used to treat onchocerciasis and lymphatic filariasis in millions of people worldwide, as part of a global drug donation programme. Since its development, nearly 3.7 billion dosages of ivermectin have been distributed in mass drug administration campaigns globally. Presently, ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and scabies.³

The use of ivermectin as a therapeutic treatment option for viral infections has been studied in the past, with in

vitro data showing some activity against a broad range of viruses, including HIV-1, Dengue, Influenza and the Zika virus.⁴ In a study conducted by Wagstaff et al. in 2012, the in vitro nuclear transport inhibitory properties of ivermectin, a broad-spectrum inhibitor of importin α/β nuclear transport, has been demonstrated without any effect on a range of other nuclear transport pathways, including those mediated by importin $\beta 1$ alone. However, more importantly, the study established the potent antiviral activity of ivermectin against both HIV-1 and Dengue virus, both of which are strongly reliant on importin α/β nuclear transport, with respect to the HIV-1 integrase and NS-5 (non-structural protein 5) polymerase proteins respectively. Furthermore, ivermectin has been shown to be a potent in vitro inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), showing a 99.8% reduction in viral RNA after 48 hours.^{5,6} However, in vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not previously been reported.

In 2020, an Australian publication by Caly et al. sparked global interest in ivermectin for the treatment of SARS-CoV-2.⁷ The study revealed that ivermectin 5 μM inhibited SARS-CoV-2 for up to 48 hours in vitro, which correlated with other studies done earlier.⁸ Currently, there is no proven effective anti-viral treatment for COVID-19. Thus, the race is on to find appropriate treatment options, especially because up to 10% of COVID-19 patients present with severe illness.⁹

South Africa is in the grips of a second wave of the COVID-19 pandemic and is currently facing mounting pressure from both the public, and members of the healthcare sector alike, to consider making ivermectin available as a potential treatment option against the SARS-CoV-2 virus. It is therefore crucial for pharmacists to have the latest information at their disposal.

What is ivermectin?

Ivermectin is a 16-membered macrocyclic lactone that is derived from the Gram-positive soil bacterium, *Streptomyces avermitilis*.^{10,11} It is a semi-synthetic derivative of avermectin B_{1a}.^{12,13} This bacterium was isolated from golf course soil in Japan in 1976 and subsequent analysis revealed its potent anthelmintic ability. It displays effectiveness at low dosages, whether administered orally, topically or parenterally. It has a broad spectrum of activity against nematodes and arthropods.¹³

Additionally, the success of the drug against the horse nematode, *Onchocerca cervicalis*, resulted in its use against *O. volvulus* in humans, which causes river blindness (onchocerciasis) and which is especially prevalent amongst rural African communities.^{12,14}

Currently, ivermectin is registered for human use in several countries across the globe (such as Australia, France, the USA, Japan, and the Netherlands) for the treatment of infections such as onchocerciasis, other filarial infections and treatment-resistant scabies. For illustrative purposes, ivermectin dosages range from 150 µg/kg once-off, to three times yearly for the treatment of onchocerciasis, whilst in the treatment of scabies, it is used as a single dose of 200 µg/kg, and sometimes followed by two or three repeat dosages that are separated by one- or two-week intervals.¹² In the case of lymphatic filariasis, the dosage is 400 µg/kg once-off.¹⁵

Ivermectin is not currently registered in South Africa, but may be obtained on a named-patient basis with the approval of the local regulatory body, the South African Health Products Regulatory Authority (SAHPRA).¹⁵ Ivermectin has been described as a so-called wonder drug and excitement around repurposing this drug for new disease indications has generated a lot of research interest globally. There has been interest in the drug being used in treatment of malaria, schistosomiasis, myiasis, rosacea, leishmaniasis, trichinosis, bedbugs, African trypanosomiasis, asthma, for anti-cancer and neurological disease indications, and as an antiviral agent (for example, in the treatment of Dengue fever and HIV-1 infection).⁶

It is of interest to note that ivermectin, and other closely related avermectins, have been in use in veterinary practice for decades. Ivermectin is indicated for a wide variety of parasitic roundworm infections, to treat infestations with most mites and lice species, and against several types of myiasis (i.e. when developing fly larvae infest the skin), in

livestock, poultry and even in household pets (including birds). It is, however, toxic to fish and other forms of aquatic life, as well as to honeybees and many other insects (with the latter being implied by the fact that another avermectin, namely abamectin, is an agricultural pesticide). Several different dosage forms are available to treat specific species of animals or for specific indications. These include drenches, feed additives, oral solutions, pour-on formulations, injectables, oral tablets, etc. It is crucial for humans not to use products that have been tested and registered for use in animal species, and especially, that humans do not ingest any formulation that has otherwise been developed for topical or parenteral administration only. Moxidectin is classified as a second-generation macrocyclic lactone endectocide with potent activity.^{13,16,17}

Safety profile of ivermectin

Ivermectin has been shown to be safe in pregnant women and children, while in adults, several studies described only mild to moderate side-effects such as skin rash, fever, headache, nausea, vomiting, diarrhoea, stomach pain, facial and limb swelling, a sudden drop in blood pressure, liver injury and dizziness, but nothing that was considered to be life-threatening.¹⁸⁻²³ However, the concomitant use of alcohol is not recommended. The administration of anti-tuberculosis drugs and cholera vaccines is contra-indicated with ivermectin, and the use of warfarin in combination with ivermectin requires careful dose monitoring.²⁴ More pronounced neurotoxicity could occur; however, this is considered to be a rare adverse effect.²⁴ What is important to note, though, is the fact that these side-effects occur at lower dosages and that there is insufficient data to recommend higher than the approved dosages at the present time.³

Regulatory framework for medicine registration in South Africa

SAHPRA, as per the Medicines and Related Substances Act (Act No 101 of 1965 as amended) and the Hazardous Substances Act (Act No 15 of 1973), is responsible for regulating all health products in South Africa. This includes the monitoring, evaluating, investigating and registration of medicines, medical devices, clinical trials, complementary medicines and in vitro diagnostic devices (IVDs). Their foremost priority is to protect the health and well-being of South Africans by ensuring the safety, efficacy and quality of medicines, medical devices and IVDs.²³

Furthermore, the National Drug Policy states that only South African registered medicines may be imported, produced, stored, exported and sold within the boundaries of the Republic. Licenses will be provided to companies that wish to register their products in South Africa, provided they comply with the Good Manufacturing Practice (GMP) requirements, as well as all of the applicable regulations.²⁵

As per the Medicines and Related Substances Act 101 of 1965, Section 2B (1), SAHPRA must:

- Ensure the efficient, effective and ethical evaluation or assessment and regulation of medicines, medical devices, radiation emitting devices and radioactive nuclides that meet the defined standards of quality, safety, efficacy and performance, where applicable.
- Ensure that clinical trial or clinical performance study protocols are assessed according to prescribed scientific, ethical and professional criteria and defined standards.
- Ensure that compliance with existing legislation is promoted and achieved through a process of active inspection and investigation.

Furthermore, SAHPRA must:

- Liaise with any other regulatory authority or institution and may, without limiting the generality of this power, require the necessary information from, exchange information with, and receive information from any such authority or institution in respect of:
 - matters of common interest; or
 - a specific investigation.

Currently, in South Africa, ivermectin is registered only for animal use as an anti-parasitic agent in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947) and is prescribed by veterinarians or other suitably trained personnel.²³

SAHPRA has granted Section 21 permits for the topical use of ivermectin, as an unregistered product, on a per-patient basis for the treatment of conditions such as scabies or headlice. SAHPRA has to provide the approval for the importation of an unregistered drug, which has approval in other countries.²³

On 22 December 2020, SAHPRA provided the following statement on ivermectin in relation to its use in the management of COVID-19:²³

“Ivermectin is not indicated nor approved by SAHPRA for use in humans. There is no confirmatory data on ivermectin available as yet for its use in the management of COVID-19 infections. In terms of safety and efficacy there is no evidence to support the use of ivermectin and we do not have any clinical trial evidence to justify its use.”

However, this has been revised on 27 January and SAHPRA announced:

“That they will facilitate a controlled, compassionate, access programme for Ivermectin.”

The authority has, however, welcomed applications for clinical trials on ivermectin and is committed to expedite any of the processes required to assist in this matter.

Further to this, the COVID-19 Subcommittee of the National Essential Medicines List Committee (NEMLC) and the Ministerial Advisory Committee (MAC) on COVID-19 have both provided reports stating that there is insufficient evidence to support the use of ivermectin in the treatment of COVID-19 at this time.^{26,27}

Roles and responsibilities of the pharmacist

Recently, the pharmacy profession has embraced a more patient-centred care approach and given patients the freedom to make informed decisions about their health. However, this level of independence given to patients creates expectations and as a result places the pharmacist in an ethical dilemma.²⁸ In the rush to find an appropriate treatment for COVID-19, pharmacists in South Africa may find themselves being ethically challenged as the pressure from patients or certain groups of doctors and lobbyists, to obtain and dispense the unregistered ivermectin for human use, or even one of the registered animal ivermectin products, keeps on mounting.^{29,30} In a recent news report, it was reported that a pharmacist had landed in hot water for violating the Medicines and Related Substances Act 101 of 1965 by allegedly dispensing ivermectin to a patient.³⁰

Pharmacists and other pharmacy personnel need to be cognisant of a few aspects in relation to dispensing unregistered medicines or medicines not suitable for human use:

- In terms of Section 22A (5) and (6) of the Medicines and Related Substances Act, 101 of 1965, any medicine that falls under Schedule 3 or higher may only be dispensed on presentation of a valid prescription. Pharmacists and pharmacy support personnel who are found to have dispensed Schedule 3 or higher medicines without valid prescriptions will face disciplinary action in terms of Chapter V of the Pharmacy Act, 53 of 1974.³¹
- According to the ethical rules and code of conduct: “A pharmacist must at all times exercise proper and/or reasonable care in respect of and control over medicines.” The pharmacist must ensure that a medicine registered with SAHPRA must have the relevant registration number displayed on each pack or container. A pharmacist must not accept medicinal products that are not so labelled.³²
- The purchase, possession, sale, supply or dispensing of an unregistered medicinal product, except where specifically permitted by legislation, is considered by Council to be unprofessional conduct, and subject to disciplinary action by Council in terms of Chapter V of the Pharmacy Act.³²

Evidence available on ivermectin use in COVID-19

Currently, the data pertaining to the in vivo use of ivermectin, repurposed for COVID-19, is based on observational, retrospective, narrative reviews and two small randomised controlled trials (RCTs).^{5,10,24,33-56} The pressure is mounting

from social media platforms, at least one group of doctors, and the public, to have ivermectin made available in the management of COVID-19. The evidence for the use of ivermectin in COVID-19 has been reviewed by the South African National Department of Health (SA-NDoH), SAHPRA, and the MAC on COVID-19, and the following conclusions were made:^{23,26,27}

- **SA-NDoH:** There is a paucity in evidence for the repurposing of ivermectin for the treatment of COVID-19. The two small early phase RCTs of ivermectin versus placebo that constitute the current bulk of the available evidence, had significant methodological shortcomings. Despite this fact, there seems to be no clear benefit to ivermectin with respect to viral load reduction or the improvement of clinical outcomes. From a safety stance, the effective concentrations and the relevance of in vitro concentrations against SARS-CoV-2 need to be determined, and these concentrations should be achieved in vivo with few adverse events. The final conclusion is that the current body of evidence does not support the use of ivermectin as an antiviral agent, except in a clinical trial setting.
- **SAPHRA:** The regulatory body also noted that the overall quality of RCTs of ivermectin in the treatment of COVID-19 patients is poor and the existing trials are underpowered and poorly designed. Similar to the rapid review done by the SA-NDoH, they included the evidence provided by the Front Line COVID-19 Critical Care Alliance. SAPHRA has indicated that it would welcome and fast-track an application for a suitable RCT.
- **MAC:** The committee made the following recommendations based on the evidence above:
 - Until more robust evidence is available, the routine use of ivermectin for either the prevention or treatment of COVID-19 is not justified.
 - Nonetheless, emerging evidence must be actively sought and carefully reviewed. Reports of clinical trials of ivermectin for the prevention or treatment of COVID-19 must be closely watched, as they become available. As always, reports in peer-reviewed publications will be preferred.
 - Effective messaging needs to be developed to communicate both to the general public and to health professionals that the use of unregulated products purporting to contain ivermectin is risky and unethical at this stage.
 - Unregulated distribution channels are at risk of the introduction of sub-standard and falsified products, which can be deleterious to human health.

Conclusion: the way forward for ivermectin and COVID-19

Currently, the evidence pertaining to the use of ivermectin does in fact “demonstrate a strong signal of therapeutic

efficacy” in COVID-19. Ivermectin is an anti-parasitic medication that is widely used in low- and middle-income countries to treat parasitic worm infections in adults and children. Having been used for decades for this purpose, it is considered safe and effective and has an increasing list of possible indications due to its antiviral and anti-inflammatory properties. On the World Health Organization’s Model List of Essential Medicines, it is retained in the form of a 3 mg tablet. For parasitic infections in adults, ivermectin is commonly administered as a single 12 mg oral dosage (0.2 mg/kg). However for the indication in COVID-19, the ideal dose for ivermectin has also not been finalised, and should be part of the evidence required from clinical trials. As the in vitro data should correlate to clinically achievable plasma levels. According to the website, <https://clinicaltrials.gov>, as of 21 December 2020, a total of 37 clinical trials to investigate the role of ivermectin (in various dosage forms) in the prevention and treatment of COVID-19, have been registered on this mandatory platform. At least eight of these seem to have been completed to date, and the forthcoming publication of the relevant study results is being eagerly anticipated.^{43-56,58}

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