health
Department:
Health
REPUBLIC OF SOUTH AFRICA

INTERNAL MEMO

Date:	07 January 2021		
To:	**The Honorable Dr ZL Mkhize, Minister of Health**	From:	**Ministerial Advisory Committee (MAC) on COVID-19**

IVERMECTIN FOR THE TREATMENT OF COVID-19

Background

The use of ivermectin for the treatment of prevention of COVID-19 has generated significant global interest. The use of this repurposed medicine is being heavily promoted via social media. However, given the limited evidence of efficacy and safety, as well as appropriate dosing of ivermectin, its place in therapy and prophylaxis remains uncertain at this point.

Problem Statement

- Clinicians, COVID-19 patients and the general public perceive an urgent need for effective means to both prevent and treat the condition. This need is amplified by the perceived delay in access to vaccines, which are only likely to become available in South Africa in the second quarter of 2021. Clinicians are in need of effective management options for COVID-19, especially in ambulatory care (before patients are admitted to hospital, or where admission is delayed or difficult). As a result, motivated by concern for their patients, clinicians are grasping at any option which promises positive results. Ivermectin is being portrayed, despite the lack of high-quality evidence, as one such option. It has therefore been observed that unregulated use of ivermectin is evident in South Africa and increasing.

- Ivermectin is registered in South Africa in terms of the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act (Act 36 of 1947) for the treatment of parasites in animal. No ivermectin-containing medicine for human use is registered in South Africa. Access to ivermectin for human use is only possible in terms of section 21 of the Medicines and Related Substances Act (Act 101 of 1965). In individual cases, the South African Health Products Regulatory Authority (SAHPRA) provides approval for the importation of a drug not registered in South Africa, but which is licensed in other countries. For example, permission has been granted for access to ivermectin for the treatment of severe, crusted scabies. To date, SAHPRA has received no applications for clinical trials involving ivermectin nor for the registration of any ivermectin-containing medicine for the treatment or prevention of COVID-19. Using medicines not approved by SAHPRA is illegal.

- There is some *in vitro* evidence that ivermectin has antiviral activity against SARS-CoV-2. Other host-directed effects may also be possible. Ivermectin has been used, at various doses and in combination with other medicines, in a number of clinical studies, both observational and randomized. The currently available data have been reviewed by the National Essential Medicines Committee COVID-19 Subcommittee and by SAHPRA but are considered insufficient to justify safe use in clinical practice at this point. The Access to COVID-19 Tools (ACT) Accelerator has also commissioned a systematic review and meta-analysis of the available clinical trials evidence, but that process has yet to be concluded (Hill *et al*.). More data is required from adequately powered, well-designed randomized clinical trials to demonstrate the efficacy and safety of ivermectin in both treatment and prevention of COVID-19. Some larger trials are ongoing, and it is hoped that the results will become available within the first quarter of 2021.

- At a community level it appears that ivermectin is being widely promoted for the treatment and/or prevention of COVID-19. There are numerous anecdotal reports from general practitioners and pharmacists of the widespread prescribing and sale of ivermectin for these purposes. Different dosages and dosage forms are being used, including those compounded from available veterinary products. No meaningful clinical data can be collected from this type of unregulated, off-label use. The vast majority of patients with COVID-19 will recover without specific pharmacological treatment.

- There have been reports of apparent toxicity from overdoses of ivermectin. Although portrayed as safe, ivermectin is associated with a range of adverse effects when used in its registered indications in humans.

- There also appears to have been some importation of ivermectin products from other countries, without regulatory approval, as well as diversion from veterinary use. Of great concern, there are reports of profiteering from the sale of these unlicensed products which purport to contain ivermectin. Prices as high as R500 per tablet have been reported. There is also anecdotal evidence that ivermectin is distributed for free in KwaZulu-Natal. SAHPRA is investigating complaints of unregulated sale and use of ivermectin products.

- There are growing demands for access to ivermectin from certain sectors of civil society, including a demand that SAHPRA should register ivermectin for human use in terms of Act 101. SAHPRA cannot do so in the absence of an application for registration, accompanied by sufficient evidence of quality, safety and efficacy. Nonetheless, access for individual named patients can be allowed in terms of section 21, provided that evidence of possible benefit is provided and a risk-benefit analysis supports such an application. SAHPRA's statutory function is as a guardian of the safety of the South African public and premature support of a medicine with unproven safety and efficacy information is difficult to justify.

- The argument that medicine found to be safe in other conditions can be used for COVID-19 before the arrival of adequate COVID-specific safety and efficacy data is not sound. For example, while chloroquine and azithromycin are both individually safe medicines, their use in severely ill COVID-19 patients with multiple comorbidities is now associated with emerging signals of possible harm.

Evidence Review

- There is insufficient evidence at this stage to support the routine use of ivermectin for either the prevention or treatment of COVID-19.

- As noted by SAHPRA on 6 January 2021, the overall quality of randomised controlled clinical trials of ivermectin in the treatment of COVID-19 patient is poor and the existing trials are underpowered and poorly designed. This includes the evidence provided by the Front Line COVID-19 Critical Care Alliance. That evidence is also being assessed by the team commissioned by the ACT-A (Hill *et al*.) and a final report of that systematic review and meta-analysis is expected to be released in the week of 11 January 2021. SAPHRA has indicated that it would welcome and fast track an application for a randomized controlled trial.

- The rapid review of the available evidence conducted by the National Essential Medicines List Committee (NEMLC) COVID-19 Subcommittee, which relied on the existing living review by the COVID-NMA, suggested that ivermectin not be used for the treatment of patients with COVID-19, as the evidence of efficacy and safety is uncertain at this point. Nonetheless, the NEMLC COVID-19 sub-committee is actively reviewing all available evidence, and will continue to review emerging evidence from clinical trials that are ongoing. As of December 2020, there were 37 trials registered on Clinicaltrials.gov.

Recommendations

- 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.

Thank you for consideration of this request.

Kind regards,

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CO-CHAIRPERSONS: MINISTERIAL ADVISORY COMMITTEE ON COVID-19
DATE: 7 January 2021
CC:

- **Dr S Buthelezi (Director-General: Health)**
- **Dr T Pillay (Deputy Director-General)**
- **Incident Management Team**