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Health  
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**INTERNAL MEMO**

Date:	18 June 2020		
To:	<b>Minister ZL Mkhize, Honorable Minister of Health</b>	From:	<b>Ministerial Advisory Committee (MAC) on COVID-19</b>

**USE OF DEXAMETHASONE FOR THE TREATMENT OF SEVERE COVID-19**

**Problem statement**

- Following the release of findings from the RECOVERY trial, should South Africa consider the use of dexamethasone for the treatment of severe COVID-19?

**Evidence:**

The use of corticosteroids for the treatment of COVID-19 in South Africa is currently defined in the National Department of Health’s *Clinical Management of Suspected or Confirmed COVID-19 Disease (version 4, 18th May 2020)* as follows:

**Do not routinely give systemic corticosteroids for treatment of COVID-19 unless they are indicated for another reason.**

*Corticosteroid use has been associated with various deleterious effects in related viruses.<sup>1</sup> Their use in influenza has been associated with an increased risk of mortality, a higher rate of secondary infections, and a greater length of Intensive Care Unit (ICU) stay.<sup>2,3</sup> A systematic review of observational studies of corticosteroids administered to patients with severe acute respiratory syndrome (SARS) reported no survival benefit and probable harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance).<sup>4</sup> A recent study of patients receiving corticosteroids for Middle East Respiratory Syndrome (MERS) used a similar statistical approach and found no effect of corticosteroids on mortality but delayed lower respiratory tract (LRT) clearance of MERS-CoV.<sup>5</sup> The effects of corticosteroid administration on patients with COVID-19 has not been adequately studied, but as with MERS and SARS, corticosteroid use has been associated with delayed viral clearance when used in COVID-19 patients.<sup>6</sup> Given the lack of effectiveness and possible harm previously seen, routine corticosteroids should be avoided unless they are indicated for other reasons, such as an asthma or Chronic Obstructive Pulmonary Disease (COPD) exacerbation.*

*The role of corticosteroids in patients with COVID-19 and refractory shock remains to be clarified. Surviving Sepsis guidelines for COVID-19 provided a weak recommendation, based on “very low quality evidence”, for low-dose corticosteroids in patients with refractory shock*

(e.g. hydrocortisone 200mg daily in adults).<sup>7</sup> This was extrapolated from a 2018 systematic review of corticosteroids in adults with septic shock demonstrating an average one-day shorter ICU stay but no effect on mortality.<sup>8</sup>

The COVID-19 National Essential Medicines List (NEML) Therapeutic Guideline's Subcommittee is currently updating their recommendations on the use of corticosteroids in COVID-19.

On Tuesday 16<sup>th</sup> June 2020, a statement was issued from the chief investigators of the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial, a United Kingdom (UK)-based adaptive trial of various potential treatments for COVID-19, one of which was dexamethasone.

The dexamethasone arm of the trial compared dexamethasone 6mg po or iv once daily for 10 days against standard of care.

*“A total of 2104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomised to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).*

*Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; p=0.14).*

*Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.”*

#### **References**

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6. Xu K, Chen Y, Yuan J, Yi P, Ding C, Wu W, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19. *Clinical Infectious Diseases*. 2020.
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8. Rygard SL, Butler E, Granholm A, Moller MH, Cohen J, Finfer S, et al. Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2018;44(7):1003-16.

## Recommendations

### How should this statement effect the management of COVID-19 in South Africa?

- The full publication of this part of the RECOVERY trial is eagerly awaited. There are important aspects of the results that will be needed to make a full assessment of the data, none more so, than the number and type of adverse events in the dexamethasone arm versus standard of care. This is critical information needed to provide definitive guidance.
- In the interim, it is believed that oral or intravenous dexamethasone 6mg daily for 10 days may be considered in patients with a confirmed diagnosis of COVID-19 who are being mechanically ventilated. Albeit a seeming lesser effect from dexamethasone in those patients requiring oxygen but not being mechanically ventilated, we also advise that dexamethasone may be considered for patients admitted to hospital with COVID-19 requiring oxygen support but not being mechanically ventilated, especially those requiring high flow nasal oxygen, Continuous Positive Airway Pressure (CPAP), or non-invasive ventilation.
- Patients admitted to hospital with a confirmed or suspected diagnosis of COVID-19 who do not require oxygen support should not receive dexamethasone or other steroid unless clinically indicated for a specific comorbidity.
- Contraindications to dexamethasone and adverse effects are detailed in the EML and South African Medicines Formulary (SAMF), and clinicians are encouraged to refer to these resources.
- As oral dexamethasone is a Section 21 medicine, equivalent corticosteroid may be used where dexamethasone is unavailable. The RECOVERY trial included prednisone in pregnant women, and this is one oral option (a dose of 40mg prednisone was used in the trial). Betamethasone is a further oral option.
- **It must be stressed that this advisory is based on a preliminary statement by the Chief Investigators of the RECOVERY Trial, and this advisory may be subject to change following review of the full publication.**

Thank you for your kind consideration of this advisory from the MAC on COVID-19.

Kind regards,



**PROFESSOR SALIM S. ABDOOL KARIM**

**OVERARCHING CHAIRPERSON: MINISTERIAL ADVISORY COMMITTEE ON COVID-19**

**DATE: 18 June 2020**

#### CC:

- » **Dr S Buthelezi (Director-General: Health)**
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