Department of Health & Social Care

MHRA

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2020/033 03 September 2020

This alert replaces the previously issued alerts regarding Dexamethasone in the use of COVID-19. The most recent of which, CEM/CMO/2020/026 was published on 16 June.

Corticosteroids in the treatment of suspected or confirmed COVID-19

Implementation and management of supply for treatment of suspected or confirmed COVID-19

Summary

For immediate action

Corticosteroids, and in particular dexamethasone and hydrocortisone, have been demonstrated to have a place in the management of patients with COVID-19. Following recent publication of the REMAP-CAP trial for hydrocortisone and a meta-analysis of corticosteroids, the World Health Organization (WHO) has recently issued new interim guidance recommending the use of systemic corticosteroids in severe and critical COVID-19 disease.

The revised WHO recommendations for the use of dexamethasone or hydrocortisone in the management of patients with severe or critical COVID-19 are provided below. Please see the footnotes for WHO definitions of 'severe[1]', 'critical[2]' and 'non-severe[3]' COVID-19.

The WHO guidance makes two recommendations:

1. a strong recommendation for systemic (intravenous or oral) corticosteroid therapy in patients with severe[1] and critical[2] COVID-19, and
2. a conditional recommendation not to use corticosteroid therapy in patients with non-severe[3] COVID-19.

It should be noted that the WHO guidance is intended to apply globally, and that healthcare conditions can vary significantly from country to country. In the UK setting, the WHO guidance is likely to apply primarily to patients with COVID-19 who are hospitalised and receiving supplemental oxygen. However, there may be occasions when UK patients with COVID-19

[1] The WHO defines severe COVID-19 as any of the following: (1) oxygen saturation < 90% on room air, (2) respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old. (3) signs of severe respiratory distress (i.e. accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).

[2] The WHO defines critical COVID-19 as: acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

[3] The WHO defines non-severe COVID-19 as the absence of any signs of severe or critical COVID-19.

meet the WHO criteria of severe or critical but are not hospitalised, in which case the WHO guidance for treatment would apply.

Clinical Guidance

The approach to utilisation of corticosteroids in COVID-19 is informed by the extensive experience of the use of this class of medicines for other indications and the information from the REACT meta-analysis where a clinical benefit was demonstrated. The REACT study includes results from seven randomised controlled trials (RCTs), including the RECOVERY and REMAP-CAP trials.

Corticosteroids are indicated for the treatment of suspected or confirmed COVID-19 for:

- Patients with severe[1] or critical[2] COVID-19 as defined by the WHO
- For information on use in children, pregnant or breastfeeding women, please refer to the Summary of Product Characteristics (SPC) for dexamethasone and hydrocortisone.

For **dexamethasone** the recommended adult dose schedule (as applied from the WHO guidance) is:

- For dexamethasone 2mg tablets: dosage three tablets once a day for 7-10 days[4]
- For dexamethasone 2mg/5mL oral solution: dosage 15mL once a day for 7-10 days
- For dexamethasone 3.3mg/mL intravenous 1ml ampoules: dosage 1.8mL (5.94mg) once a day for 7-10 days
- Treatment should stop if discharged from hospital within the 10 days

For patients able to swallow and in whom there are no significant concerns about enteral absorption, tablets should be prescribed. IV administration should only be used where tablets or oral solution are not appropriate, or not available.

When prescribing dexamethasone consideration needs to be given to the gastric ulcer protection effect of proton pump inhibitors according to local hospital policy.

For **hydrocortisone** the recommended adult dose schedule (as applied from the WHO guidance) is:

- 50mg hydrocortisone administered intravenously three times per day for 7-10 days[5]
- A longer low dose duration can be considered for patients with septic shock[6]

The guidance issued in this CAS alert builds on the previous related CAS alert, by now including intravenous hydrocortisone and aligning with the new WHO guidance. Physicians may wish to note that the majority of evidence in the published meta-analysis emanates from the assessment of dexamethasone in the RECOVERY trial. Currently there are no data directly comparing dexamethasone and hydrocortisone.

Patients with non-severe COVID-19

The WHO definition for patients with non-severe COVID-19 is the absence of any signs of severe[1] or critical[2] COVID-19. A conditional recommendation has been made by WHO not to use corticosteroid therapy in patients with non-severe[3] COVID-19.

[4] In the RECOVERY trial the dose schedule was 6mg once per day for 10 days

[5] In the REMAP-CAP trial the dose schedule was 50mg administered intravenously four times per day for 7 days

[6] As per findings from the REMAP-CAP trial, low dose administration may be continued for up to a maximum of 28 days in the presence of septic shock (the REMAP-CAP trial has not demonstrated evidence in the use of a higher dose)

Licences

The use of dexamethasone and injectable formulations of hydrocortisone in severe[1] or critical[2] COVID-19 is within the medicines' licensed indications.

Coadministration

Remdesivir is currently available under a published interim clinical commissioning policy.

Coadministration of dexamethasone or hydrocortisone with remdesivir has not been fully studied but based on metabolism and clearance a clinically significant interaction is unlikely (University of Liverpool COVID-19 Drug Interactions link).

Dexamethasone and hydrocortisone are substrates of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after i.v administration, remdesivir is unlikely to have a significant effect on dexamethasone or hydrocortisone exposure. Neither dexamethasone nor hydrocortisone are likely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

Medicine supply

Hospitals should use existing supplies of dexamethasone or hydrocortisone, including any remaining stock from the RECOVERY trial. If required, hospitals should order further stock from their usual supplier but must not order more than 2 weeks expected demand at a time.

Data collection

Safety reporting

Any suspected adverse drug reactions (ADRs) for patients receiving corticosteroids for this indication can be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

Clinical Outcome reporting

The Deputy Chief Medical Officer recommends that data on all patients with COVID-19 should be captured through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (link to forms).

Action

Clinical Teams should:

- work with their hospital chief pharmacist to secure readiness to offer dexamethasone or hydrocortisone with immediate effect;
- develop and implement local policies for the use of systemic corticosteroids, namely dexamethasone and hydrocortisone.

Pharmacy leads (Regional Pharmacy Procurement Leads in England) should:

- manage available supplies;
- work with hospitals who have stock holding beyond their projected demand to re-distribute this stock across their region.

Trust/Hospital Chief Pharmacists should:

- manage stock appropriately (in England working with Regional Chief Pharmacists and Regional Pharmacy Procurement leads);
- order stock according to guidance.

Deadlines for actions

- Actions underway: on receipt of this alert;
- Actions complete: as soon as possible.

Supporting Information

The ISARIC 4C (Coronavirus Clinical Characterisation Consortium) can be found at: https://isaric4c.net/

NICE COVID-19 prescribing briefing: corticosteroids:

https://www.nice.org.uk/guidance/ng159/resources/covid19-prescribing-briefing-corticosteroids-pdf-8839913581

Distribution

NHS Trusts (NHS boards in Scotland and Wales)
Regional Medical Directors
Regional Chief Pharmacists
Hospital Chief Pharmacists
Trust/hospital medical directors to circulate to medical and nursing staff managing COVID-19 patients.

Enquiries

England
Enquiries from NHS trusts in England should in the first instance be directed to your trust pharmacy team who will escalate issues to the Regional Chief Pharmacist and national teams if required. Any strategic issues please contact: england.spoc-c19therapeutics@nhs.net.

Northern Ireland
Enquiries from hospitals in Northern Ireland should in the first instance be directed to your hospital pharmacy team.

Scotland
Enquiries from hospitals in Scotland should in the first instance be directed to your hospital pharmacy team who should escalate queries relating to supply to NSS.NHSSMedicineShortages@nhs.net and all other issues should be escalated to the Scottish Government's Medicines Policy Team using the email address - CPO-COVID19@gov.scot.

Wales
Enquiries from hospitals in Wales should in the first instance be directed to the health board's Chief Pharmacist who will escalate issues to the Pharmacy and Prescribing Team at Welsh Government if required. Enquiries to the Welsh Government should be directed to: COVID-19.Pharmacy.Prescribing@gov.wales.