Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

CEM/CMO/2021/018 04 November 2021

Casirivimab and imdevimab in the treatment of COVID-19 in hospitalised patients

Summary

Neutralising monoclonal antibodies (nMABs) bind to specific sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into cells and therefore inhibiting its replication. Ronapreve® is a combination nMAB containing equal amounts of casirivimab and imdevimab.

The RECOVERY trial has demonstrated that the casirivimab and imdevimab combination reduces the relative risk of mortality by 20%, and the absolute risk of mortality by 6%, in hospitalised patients with COVID-19 who have not mounted an antibody response of their own to the virus (i.e. are seronegative[1]) at the time of treatment. Mortality was 24% in the casirivimab plus imdevimab treatment group vs 30% in those who received standard care alone. Risk of mortality in hospitalised patients has also been informed by the QCOVID® analysis.

Study 2067 (Weinrich et al, 2021), a phase 3 randomised, double-blinded, placebo-controlled trial evaluating casirivimab and imdevimab for the treatment of non-hospitalised patients with at least one risk factor for severe COVID-19, showed that the casirivimab and imdevimab combination led to a relative risk reduction for composite primary outcome of COVID-19-related hospitalisation or all-cause death through to day 29 by 70% (p=0.0024). The study showed similar treatment effects across patients treated with 2.4g and 1.2g doses of the combination.

The UK-wide clinical commissioning policy originally published on 17 September 2021 has now been revised and extends the recommendation for consideration of the intravenous use of the combination neutralising antibody casirivimab plus imdevimab in patients aged 12 and above in the following two cohorts:

1) Patients hospitalised with acute COVID-19 (total dose of 2.4g)

Hospitalised patients are eligible to be considered for casirivimab and imdevimab if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or where a multidisciplinary team (MDT) has a high level of confidence that the

[1] Refers to patients who were negative for serum anti-s spike antibodies against SARS-CoV-2

clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis
AND

- Hospitalised specifically for the management of acute symptoms of COVID-19
  AND
- Negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2

2) Patients with hospital-onset COVID-19 (total dose of 1.2g)

Patients are eligible to be considered for casirivimab and imdevimab if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test **within the preceding 72 hours** or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis
  AND
- Hospitalised for indications other than for the management of acute symptoms of COVID-19
  AND
- At high risk of progression to severe COVID-19
  OR
  COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team (MDT) assessment)
  AND
- A baseline serum antibody test (anti-S) against SARS-CoV-2 prior to treatment administration has been taken *(the result does not need to be awaited prior to treatment as it does not affect eligibility in this cohort)*

Please refer to the published policy for further details and additional guidance.

The casirivimab and imdevimab combination is licensed[2] in Great Britain for the treatment of COVID-19 in individuals aged 12 and above and weighing at least 40 kg but the published policy recommendation for use at a dose of 2.4g is an off-label use. A temporary regulation 174 approval is in place to cover use in Northern Ireland, pending a licensing decision by the European Medicines Agency (EMA).

[2] The conditional marketing authorisation covers use in Great Britain. A parallel regulation 174 approval covers use in Northern Ireland, ahead of the European Medicines Agency's determination.

Action

NHS acute trusts / health boards are asked to take the following immediate steps to support the treatment of patients admitted to hospital for the management of symptoms of COVID-19 infection:

1. **Organisations are recommended to consider prescribing the casirivimab and imdevimab antibody combination to patients aged 12 and over (and weighing at least 40 kg) in line with the published policy *to:***

    - Patients hospitalised for acute COVID-19 illness: treated at the **off-label** dose of 2.4g
    - Patients with hospital-onset COVID-19: treated at a dose of 1.2g, in line with the conditional marketing authorisation / regulation 174 approval (in Northern Ireland)**.**

    In the absence of a confirmed virological diagnosis, the treatment should only be used when a multidisciplinary team has a high level of confidence that the clinical and radiological features suggest that COVID-19 is the most likely diagnosis.

2. As nMAB therapies should be given to eligible patients as early as possible to maximise benefit, **organisations should ensure that anti-s spike antibody testing[3] is undertaken for all patients hospitalised due to COVID at, or as soon as possible after, the point of admission**. **Patients with hospital-onset COVID treated with an nMAB should also be antibody tested, with appropriate consent, to support further treatment evaluation and surveillance *(antibody status does not affect treatment eligibility in this, second, cohort)*.** If there are concerns or questions around laboratory sensitivity or thresholds these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from external quality assessment (EQA) scheme participation. Supporting laboratory networks should ensure that the maximum turnaround time for anti-s antibody tests is no greater than 24 hours from the sample being taken to the result being returned. Positive and negative antibody tests should be reported via the Second Generation Surveillance System (SGSS) to enable reimbursement of associated assay costs in England (parallel reimbursement will be available in the other devolved administrations).

3. **Treating clinicians are asked to support additional testing or data requirements where requested under country specific or UK wide surveillance programmes, in line with current guidance.**

4. Discharge letters to primary care should explicitly record that the casirivimab plus imdevimab combination has been given, together with the dose and date of administration. The following **SNOMED codes should be used to support evaluation and to inform subsequent treatment decisions**:

[3] Patients may be tested for anti-S1 or anti-S2 antibodies using any validated quantitative or qualitative anti-S assay that measures either IgG or total antibody levels. Serostatus should be established in line with the pre-determined thresholds relevant to the assay being used by the testing laboratory. Quantitative assays with pre-specified thresholds for seropositivity should return clear binary (i.e. either 'negative' or 'positive') results based on these thresholds. For quantitative assays without a formal threshold for serostatus, clinical decision-making should guide treatment decisions.

Procedure code: 47943005 |Administration of anti-infective agent (procedure)|

Presentations:

- Casirivimab 300 mg per 2.5 mL (120 mg/mL) with Imdevimab 300 mg per 2.5 mL (120 mg/mL) 2 vial pack - 40025711000001108
- Casirivimab 1332 mg per 11.1 mL (120 mg/mL) with Imdevimab 1,332 mg per 11.1 mL (120 mg/mL) 2 vial pack - 39654011000001101

5. Any organisation treating patients with the casirivimab and imdevimab antibody combination as an off-label product will be required to assure itself that the necessary internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board / trust drugs and therapeutics committee, or equivalent.

6. Organisations should adhere to the procedures outlined in the institutional readiness document which has been developed by the Specialist Pharmacy Service to support product storage, preparation and administration.

7. In England, trusts who have not yet done so should register (by site) to participate in COVID-19 specific casirivimab and imdevimab supply arrangements, via Blueteq™. Blueteq should also then be used to confirm pre-authorisation for individual patients. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest. In Scotland, Health Board Directors of Pharmacy should notify NHS National Procurement if they wish to participate. Health Boards in Wales should notify the All Wales Specialist Procurement Pharmacist of their intention to participate.

8. Organisations should note that following initial nationally determined allocations to participating hospitals, ongoing supplies to each hospital will be replenished on the basis of relative use / need. Ongoing ordering will be through existing (business as usual) routes, supported by volume-based caps (reflecting estimated eligible admissions) where required.

9. Organisations should note that initial supply will be available within 'global pandemic' packaging, which differs from the planned Great Britain (GB) packaging / labelling aligned to the product's GB licence. For example, pandemic packs display a use by date 24 months from manufacture, but current GB regulatory requirements require the product is used within 12 months of manufacture. A 'Dear Healthcare Professional' letter will be available to explain any differences in packaging and supplied packs will be approved for use in both Great Britain and Northern Ireland. **To preserve available supply, hospitals must ensure that packs with shorter use by dates are used first**.

10. Regular stock updates should be provided to trust / hospital and regional pharmacy procurement lead / chief pharmacists. Hospitals should enter the product onto stock control and prescribing systems as described below:

    Casirivimab 300 mg per 2.5 mL (120 mg/mL) with Imdevimab 300 mg per 2.5 mL (120 mg/mL) with the dose description as: 2 vial pack

    AND/OR

Casirivimab 1332 mg per 11.1 mL (120 mg/mL) with Imdevimab 1,332 mg per 11.1 mL (120 mg/mL) with the dose description as: 2 vial pack

Product Details

Ronapreve® is supplied to the UK by Roche. It is a combination neutralising monoclonal antibody (casirivimab plus imdevimab) used to inhibit viral replication in individuals who have not yet mounted an adequate antibody response to the SARS-COV-2 virus following either exposure or vaccination.

The casirivimab plus imdevimab combination for intravenous and subcutaneous use is authorised for use in the treatment and prophylaxis of COVID positive individuals aged 12 and above and weighing at least 40 kg. Supply of the casirivimab and imdevimab combination is subject to the same requirements in both Great Britain and Northern Ireland, and the product information in the Summary of Product Characteristics should be considered applicable across the UK.

Prescribing

The casirivimab plus imdevimab combination product is authorised as a treatment for COVID-19 but the published policy includes an off-label use at a dose of 2.4g. As such, clinicians prescribing this treatment should follow trust / hospital governance procedures in relation to the prescribing of off-label medicines.

Further guidance on the prescribing of off-label medicines can be found below:

- https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities
- https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines
- https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Prescribing%20competency%20framework/prescribing-competency-framework.pdf

Co-Administration

The RECOVERY study demonstrated a mortality benefit for the combination of casirivimab plus imdevimab over and above standard of care in hospitalised COVID positive antibody seronegative patients. Its use should therefore be considered alongside other relevant COVID therapies (including corticosteroids, remdesivir, and tocilizumab or sarilumab) where appropriate and unless contraindicated. There is no interaction of the casirivimab plus imdevimab combination expected for either dexamethasone or hydrocortisone, remdesivir, or tocilizumab or sarilumab.

For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

The casirivimab plus imdevimab combination should not be infused concomitantly in the same IV line with other medications.

Monitoring, tracking and follow-up

Monitoring of longer-term progress is strongly recommended via recruitment of patients receiving COVID therapies to the ISARIC-CCP study.

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly record that the casirivimab plus imdevimab combination has been given together with the dose and date of administration. SNOMED codes (see action section, above) should be used in discharge letters to primary care.

Healthcare professionals are asked to report any suspected adverse reactions via the United Kingdom Yellow Card Scheme www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store8.

Distribution

- NHS Trusts (NHS boards in Scotland and Wales)
- National / Regional Medical Directors
- National / Regional Chief Pharmacists
- Lead/Senior Pharmacists and Regional Procurement Pharmacy Leads
- Trust/Hospital Pathology Directors (to circulate to pathology networks and laboratory staff)
- Trust / Hospital Medical Directors (to circulate to medical and nursing staff managing admitted patients infected with COVID-19)

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. Further information can be requested from the dedicated email address: 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 who will escalate issues to the Regional Pharmaceutical Procurement Service or Pharmaceutical Directorate at the Department of Health if required Further information can be obtained by contacting RPHPS.Admin@northerntrust.hscni.net

Scotland
Enquiries from hospitals in Scotland should in the first instance be directed to your hospital pharmacy team who will escalate issues to either NHS National Procurement or the Scottish Government's Medicines Policy Team if required. Contact should be made using the following emails: nss.nhssmedicineshortages@nhs.scot or medicines.policy@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.