Group 1 Patients
Ronapreve™ (Casirivimab and imdevimab) for patients hospitalised due to COVID-19
Guidance for use in GGC

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 reduced the relative risk of mortality by 20%, and the absolute risk of mortality by 6%, in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (i.e. were seronegative) 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.

A UK-wide clinical commissioning policy has now been published recommending consideration of the intravenous use of the combination neutralising antibody casirivimab plus imdevimab at a total dose of 2.4g (1.2g of casirivimab plus 1.2g of imdevimab) in antibody seronegative patients hospitalised for the management of symptoms of COVID 19 infection.

Eligibility Criteria

Ronapreve treatment should be given to eligible patients as early as possible to maximise benefit. The decision to treat with Ronapreve™ requires that patients are seronegative for S-antibodies to COVID-19 and testing should be undertaken and results returned before prescribing.

Patients should meet all of the eligibility criteria and none of the exclusion criteria.

Hospitalised patients (aged 12 and above) are eligible to be considered for Ronapreve™ 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 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

The casirivimab and imdevimab combination is licensed 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 recommends an off-label dose.

Exclusion Criteria

The following patients are not eligible for treatment:

- Children weighing less than 40kg
- Children aged under 12 years
- Known hypersensitivity reaction to the active substances or to any of the excipients of casirivimab and imdevimab listed in the Summary of Product Characteristics (SmPC).
- Previously received treatment in hospital with casirivimab and imdevimab at the 2.4g (combined) dose or higher

The decision to initiate Ronapreve must be made by a Consultant with experience in the management of patients with COVID. Cases meeting the above criteria **do not** need MDT discussion.

If there is clinical uncertainty regarding a patient's suitability for Ronapreve, the Consultant in charge of the patient's care must discuss the case with at least one other Consultant who has expertise in the management of COVID, for example the on call Infectious Diseases Consultant. It may be that a broader MDT discussion is required in complex cases. The summary and outcome of this discussion, along with the names of the clinicians involved in the discussion, must be clearly documented in a clinical note on Portal.

There may be exceptional clinical circumstance where Ronapreve is given outside of above criteria, for example:

- 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.
- No confirmed negative anti-spike antibody test. Such cases include patients with known underlying immune dysfunction resulting in absence of B-cell function, where delaying treatment could be detrimental to clinical outcome
- Patients receiving immunoglobulin therapy where a "false positive " S antibody can happen

In such cases a discussion with a locally arranged MDT familiar with the management of COVID pneumonitis must be documented in clinical portal and the request to treat sent to Pharmacy during working hours.

S-Antibody Seropositive Patients

There may be exceptional clinical circumstance where Ronapreve is considered for treatment of a patient who has had a seropositive S-antibody result returned on testing. At this time the limited national stock allocation is based on prevalence of seronegative patients only. Therefore these individual cases must follow the NHS GGC Unlicensed Medicines policy process to seek review and approval for use. The supply must be approved by the appropriate Clinical Director/Chief of Medicine. It is expected that a provisional ULM decision could be provided within 24 hours so as not to delay any treatments.
https://ggcmedicines.org.uk/media/uploads/policies/section_9/9.1_unlicensed_medicines_policy_-_final_1910.pdf
https://ggcmedicines.org.uk/media/uploads/policies/section_9/form_ulm1_-_final_191101.doc

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for casirivimab and imdevimab for special warnings and precautions for use.

The casirivimab and imdevimab combination is not intended to be used as a substitute for vaccination against COVID-19.

COVID-19 Vaccines

Casirivimab and imdevimab binds to epitopes on spike protein used as immunogen in all COVID-19 vaccines, therefore it is possible that casirivimab and imdevimab may interfere with the development of effective immune responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post treatment with anti-SARSCoV-2 monoclonal antibodies. Limited safety data are available from the study HV-2093where COVID-19 vaccine was permitted and no safety concerns were identified.

Pregnancy and Women of Childbearing Potential

The RECOVERY trial included women who were pregnant or breastfeeding, and no serious adverse events were reported. The SmPC for casirivimab and imdevimab states the following:

> "Pregnancy: There are no or limited amount of data from the use of casirivimab and imdevimab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. In a tissue cross-reactivity study with casirivimab and imdevimab using human foetal tissues, no binding was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing foetus. Casirivimab and imdevimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors. If a woman becomes pregnant while taking this medicine, the individual should be informed that any potential risk to the foetus is unknown."

Prescribers should discuss contraception post treatment as appropriate, taking into account the ½ life of Ronapreve components is ~30 days.

Breast-feeding

It is unknown whether casirivimab and imdevimab are excreted in human milk. A risk to the newborns/infants cannot be excluded. Maternal IgG is known to be present in human milk and any potential risk of adverse reactions from the drug in breast-feeding infants is unknown, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from casirivimab and imdevimab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. Breast-feeding mothers with COVID19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19."

S-Antibody Testing

The process for sending samples for S-antibody testing is as follows:

- Sample type is an SST Tube ie yellow (ochre) top tube.
- IgG Spike antibody testing is provided from the Biochemistry Department at the QEUH.
- Samples at sites other than QEUH should be sent to the local lab for forwarding to QEUH Biochemistry Dept.
- Samples will be run Mon-Fri 9am – 5pm and Sat-Sun 9am-1pm.
- Results will be provided the same day for samples received between these times. Samples received after 5pm at the QEUH will be analysed the following morning.
- Requests for this test can be made via TrakCare, the request item is **"Covid IgG Spike Protein Assay"** this will also enable results to be visible in TrakCare as well as clinical portal.
- Please note that the Abbott assay used within NHS GG&C has a different cut off to the assay result previously received via NHS Lanarkshire.
    - Results <50 U/mL will be reported as 'Not-Detected' ≡ Seronegative.

In immunodeficient patients on replacement immunoglobulin (intravenous or subcutaneous), the positive detection of anti-S antibodies should be regarded as a 'positive of unknown significance'. **Patients on replacement immunoglobulin testing positive only for anti-S (and negative for anti-N antibodies) should therefore be considered to be seronegative for SARS-CoV-2.** Should evidence for passive transmission of anti-N antibodies through replacement immunoglobulin emerge in the future, the detection of anti-N antibodies should also be regarded as a 'positive of unknown significance'.

In immunocompromised groups, very low 'positive' levels of anti-S antibody on a quantitative assay (within the bottom 10% of the assay's positive range (<4000 IU/ml in NHS GGC)) should be interpreted in the context of clinical decision-making and laboratory advice and a decision to treat may still be made by the MDT on a case-by-case basis.

Administration

Before prescribing, patients must fulfil the criteria defined above or have approval from a locally arranged MDT if exceptionality applies.

If Ronapreve is indicated, the clinical team looking after the patient should contact the ward clinical pharmacist in first instance to arrange a supply of Ronapreve. If no ward pharmacist available, contact main pharmacy for a named-patient supply. The indent should indicate the patient ID details including CHI and which consultant has approved its use.

Pharmacy departments will supply the vials, a 0.2 micron inline filter and a worksheet required to assemble the final infusion for administration. **These will be supplied on a named patient basis only during pharmacy opening hours.** One kit will be available in the Emergency Drug Cupboard in the event an antibody testing result has been reported after close of business at the site and there is a clinical need to treat before pharmacy opens. **Please do not contact the on-call pharmacist out of hours for supply**. Ronapreve must be stored in a fridge when not in use. Completed Worksheets should be filed in the patients notes.

Dosing

The recommended dose of casirivimab and imdevimab is 2.4g (1.2g each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion.
Please note that the use of casirivimab and imdevimab in patients hospitalised with COVID-19 is off-label at the dose recommended.

Casivirimab and imdevimab must be diluted in a single 250mL bag of 0.9% sodium chloride (do not require to remove an equivalent volume of saline) - total volume 270mL and given over a minimum of 30 minutes.

- **Casirivimab and imdevimab must not be infused concomitantly in the same intravenous line with other medication. Repeat doses should not be administered**.
- Hypersensitivity reactions, including anaphylaxis, have been reported with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.
- Infusion-related reactions (IRRs) have been observed with IV administration of casirivimab and imdevimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, IRRs may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Co-Administration

Co-administration with corticosteroids, remdesivir and IL6-inhibitors is permitted and no drug-drug interactions are expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website:
(https://www.covid19-druginteractions.org/checker).
Casirivimab and imdevimab should not be regarded as an alternative to corticosteroids.

Monitoring, tracking and follow up

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 mention that Ronapreve™ has been given and the date of administration.

There is an urgent need to generate more evidence and greater understanding around the use of nMABs in the treatment of patients with COVID-19. Both surveillance and service evaluation are necessary to gain knowledge around the following: factors of relevance in determining nMAB treatment; the impact of nMAB treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB use, such as generation of new mutations.

Treating clinicians are asked to ensure that all PCR tests undertaken as an inpatient and/or in the community where any patient who is receiving ongoing PCR testing as part of secondary care (for example, through an outpatient clinic) should do this through the hospital laboratories (WoSSVC or HUB Not Lighthouse) where these samples will be sequenced if positive– please specify 'Post mAB PCR' on the sample request form.

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