From the Chief Medical Officer
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Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

HSS(MD) 90/2021

FOR ACTION
Chief Executives, Public Health Agency/Health and Social Care Board/HSC Trusts/ NIAS
GP Medical Advisers, Health & Social Care Board
All General Practitioners and GP Locums (for onward distribution to practice staff)
OOHs Medical Managers (for onward distribution to staff)

PLEASE SEE ATTACHED FULL CIRCULATION LIST

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Our Ref: HSS(MD) 90/2021
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Dear Colleague

COVID-19 THERAPEUTIC ALERT: NEUTRALISING MONOCLONAL ANTIBODY AND INTRAVENOUS ANTIVIRAL TREATMENTS FOR PATIENTS IN HOSPITAL WITH COVID-19 INFECTION

This letter supersedes and replaces HSS(MD) 65/2021, first issued on 20 September 2021 and later addenda on 7 November 2021 and 21 December 2021

Actions required

HSC Trusts are asked to take the following immediate steps to support the treatment of patients in hospital with COVID-19 infection:

1. **Organisations are recommended to consider prescribing a monoclonal antibody or intravenous antiviral treatment for adults, and children aged 12 and over and weighing at least 40 kg, in line with the updated published policy.**

   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. **Organisations should ensure that anti-s spike antibody testing is undertaken for all patients hospitalised due to COVID-19 at, or as soon as possible after, the point of admission. Patients with hospital-onset COVID-19 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), or equivalent systems in Northern Ireland, to support surveillance and enable reimbursement of associated assay costs.

(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).

3. **Genotyping should be undertaken for all inpatients with COVID-19 infection. Requests should be marked 'urgent – treatment is variant dependent' to assist laboratories in their prioritisation.** Genotyping results should be reported via the Second Generation Surveillance System (SGSS), or equivalent systems in Northern Ireland, to support surveillance and enable reimbursement of associated assay costs.

4. **Noting the critical role of surveillance, treating clinicians are strongly encouraged to actively support additional testing or data requirements as requested under country specific or UK wide surveillance programmes, in line with further guidance to be issued.**

5. Discharge letters to primary care should explicitly record that a monoclonal antibody treatment has been given, together with the dose and date of administration.

6. Any organisation treating patients with the casirivimab and imdevimab antibody combination (Ronapreve®) or sotrovimab should note that currently available supplies are unlicensed medicines that are supplied under a Regulation 174 emergency use authorisation for use in Northern Ireland, and that use of remdesivir in children aged 12 to 17 years in line with this policy is off-label. HSC Trusts will be required to assure themselves that the necessary internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the HSC Trust's drugs and therapeutics committee, or equivalent.

7. 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.

8. HSC Trusts in Northern Ireland should liaise with the Regional Pharmaceutical Procurement Service to register interest in COVID-19 specific supply arrangements. Allocations for use within the HSC will be determined regionally, informed by nationally determined allocations, with ongoing supplies to each hospital 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 of COVID-19 medicines may be available within 'emergency supply' packaging, which differs from the planned Great Britain (GB) packaging / labelling aligned to the product's GB licence (or the equivalent product packaging / labelling aligned to a Regulation 174 authorisation or European Medicines Agency marketing authorisation as applicable in Northern Ireland). **To preserve available supply, providers must ensure that packs with shorter use by dates are used first.**

10. Provide regular updates on the stock position to HSC Trust Heads of Pharmacy and Medicines Management, pharmacy procurement leads and the Regional Pharmaceutical Procurement Service. 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

    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

    OR

    Remdesivir 100mg powder for concentrate for solution for infusion

    OR

    Sotrovimab 500mg/8ml solution for infusion vials

The Health and Social Care Board is asked to:

11. Continue to work with HSC Trusts and the Regional Pharmaceutical Procurement Service to monitor uptake of treatment, pending consideration for routine commissioning in line with extant Managed Entry arrangements.

The Public Health Agency is asked to:

12. Continue to work with HSC Trusts and the Business Services Organisation to report positive and negative tests to enable retrospective reimbursement of associated assay costs.

The previously published UK-wide interim clinical commissioning policy providing access to neutralising monoclonal antibodies (nMABs) for hospitalised patients with COVID-19 infection has now been updated to reflect the RECOVERY trial's announcement of a new sotrovimab arm for patients hospitalised due to COVID-19 and to include a new treatment option of intravenous antiviral therapy (remdesivir (Veklury®)) for patients with hospital onset COVID infection.

PCR positive antibody seronegative patients admitted to hospital due to COVID-19 infection can continue to be offered the combination monoclonal antibody casirivimab and imdevimab (Ronapreve®) only where infection with a non-Omicron variant has been confirmed through genotyping. Clinicians are encouraged to consider entering all other patients hospitalised due to COVID-19 into the RECOVERY trial, which is studying sotrovimab vs standard of care in this cohort. Genotyping of all inpatients is now recommended to assist in treatment decisions and to support wider surveillance.

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. Sotrovimab (Xevudy) is an nMAB that both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2.

Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2. Remdesivir (Veklury®) is an adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate. Remdesivir triphosphate inhibits SARS-CoV-2 RNA polymerase which perturbs viral replication.

The UK-wide clinical commissioning policy has now been revised following the publication of evidence from the PINETREE trial and the award of a marketing authorisation variation for remdesivir (Veklury®) from the European Medicines Agency (EMA)[1]. Policy amendments also reflect the rising prevalence of the Omicron variant.

Samples should be submitted for genotyping for all patients potentially eligible under the policy. Requests should be marked 'urgent – treatment is variant dependent' to assist laboratories in their prioritisation.

Patients eligible under the policy are:

GROUP 1

Patients hospitalised due to acute COVID-19 illness who are PCR positive with a non-Omicron variant and who are antibody seronegative: may be treated with a total dose of 2.4g of casirivimab and imdevimab.
Clinicians are encouraged to enter all other patients admitted to hospital due to COVID-19 infection (including those infected with the Omicron variant, regardless of

[1] Use in Northern Ireland for patients aged 18 and above is covered under the product's EMA marketing authorisation, use in patients aged 12-17 years is off label.

antibody status) into the RECOVERY trial, which is studying sotrovimab versus standard of care.

GROUP 2

Patients with hospital-onset COVID-19 (please see policy for additional criteria) who are not showing signs of clinical improvement: with confirmed Omicron infection may be treated with 500mg of sotrovimab. Where infection with a non-Omicron variant is confirmed through genotyping the patient may be treated with a total dose of 1.2g of casirivimab and imdevimab. Where the relevant nMAB is contraindicated or otherwise not possible, or there is evidence of clear clinical deterioration before genotype results are available, remdesivir may be offered at a dose of 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3.

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-19 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.

Remdesivir (Veklury®) is supplied by Gilead. Delivered intravenously, remdesivir use in Northern Ireland is covered by a European Medicines Agency marketing authorisation for 1) adults, and children aged 12 and over weighing at least 40 kg, with pneumonia requiring supplemental oxygen, and 2) for adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Sotrovimab (Xevudy®) is supplied by GlaxoSmithKline and Vir Biotechnology. Delivered intravenously, sotrovimab has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. Access to sotrovimab in Northern Ireland is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

Prescribing

The casirivimab plus imdevimab combination product (Ronapreve) and sotrovimab (Xevudy®) are unlicensed medicines which are temporarily authorised for emergency use in Northern Ireland as a treatment for COVID-19 under Regulation 174 of the Human Medicines Regulations 2012, pending issue of a conditional marketing

authorisation by the European Medicines Agency. As such, clinicians prescribing this treatment should follow HSC Trust governance procedures in relation to the prescribing of unlicensed medicines.

Remdesivir is authorised in Northern Ireland as a treatment for COVID-19 in accordance with a conditional marketing authorisation issued by the European Medicines Agency, however use in patients aged between 12 and 17 years as set out in the published policy is currently off-label. As such, clinicians in Northern Ireland prescribing this treatment should follow HSC Trust governance procedures in relation to the prescribing of off-label medicines.

Further guidance on the prescribing of off-label and unlicensed 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

There is no interaction of the monoclonal antibodies or antiviral treatments covered under the policy 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).

Monoclonal antibodies and / or antivirals 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 a monoclonal antibody has been given together with the dose and date of administration.

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 Store.

Further enquiries should in the first instance be directed to your hospital pharmacy team.

Yours sincerely

PROF SIR MICHAEL McBRIDE
Chief Medical Officer

MRS CATHY HARRISON
Chief Pharmaceutical Officer

Enclosed: Interim Clinical Commissioning Policy: Neutralising monoclonal antibodies and intravenous antivirals in the treatment of COVID-19 in hospitalised patients (published 24 December 2021)

Circulation List

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