Department of Health & Social Care

NHS

COVID-19 Therapeutic Alert

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Antivirals and neutralising monoclonal antibodies 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. Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2.

Recent evidence suggests that antivirals and nMABs significantly improve clinical outcomes in patients with COVID-19 who are at high risk of progression to severe disease and/or death.

Group 1 Patients - There are no material changes in the policy for patients who have been admitted to hospital DUE to COVID. 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 at the off-label total dose of 2.4g of casirivimab and imdevimab.

Clinicians are encouraged to consider entering all other patients admitted to hospital due to COVID infection (including those infected with the Omicron variant, regardless of antibody status) into the RECOVERY trial, which is studying sotrovimab versus standard of care. Please also refer to other published UK clinical access policies for treatment options for patients admitted due to COVID infection.

Group 2 Patients – Options for patients admitted to hospital for a non-COVID related reason but who nonetheless test positive during their hospital stay with and meeting additional eligibility criteria have been revised to provide access to an additional first-line treatment option - PF-07321332(nirmatrelvir) plus ritonavir (Paxlovid). Remdesivir (Veklury) is now a licensed second-line treatment option. Sotrovimab (Xevudy) remains available as a third-line treatment option in this cohort. Further information to support clinical decision making for patients with hospital-onset COVID-19 can be found in the supporting clinical guide.

Further details on supporting evidence and eligibility, together with further guidance, can be found in the published policy

Action

NHS acute trusts / health boards 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 an antiviral or monoclonal antibody treatment to adults, and children aged 12 and over and weighing at least 40kg, in line with the 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. PF-07321332(nirmatrelvir) plus ritonavir, and molnupiravir, are **not recommended during pregnancy.** All individuals of childbearing potential who are prescribed molnupiravir should be advised to use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. The use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment and until after one complete menstrual cycle after stopping Paxlovid.

3. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 so that they can be followed up. For more information, go to http://www.uktis.org/

4. Clinicians are encouraged to proactively support recruitment into trials developing further evidence in the treatment of COVID-19. Patients admitted to hospital due to COVID who are ineligible for the casirivimab and imdevimab combination monoclonal antibody due to confirmed infection with the Omicron variant may be considered for entry into the RECOVERY trial, which is studying sotrovimab versus standard of care.

5. **Organisations are encouraged to undertake anti-s spike antibody testing[1] for all patients hospitalised due to COVID at, or as soon as possible after, the point of admission**. **Patients with hospital-onset COVID 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 support

[1] 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.

surveillance and enable reimbursement of associated assay costs in England (parallel reimbursement will be available in the other devolved administrations).

6. **Genotyping is a key element of the management of inpatients admitted due to COVID-19 infection. Where critical to a treatment decision, genotyping 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) to support surveillance and enable reimbursement of associated assay costs in England (parallel reimbursement will be available in the other devolved administrations).

7. **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.**

8. Discharge letters to primary care should explicitly record the treatment that 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**:

Administration of Casirivimab and Imdevimab

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

Provision of PF-07321332(Nirmatrelvir) Plus Ritonavir

Procedure code: 427314002 |Antiviral therapy (procedure)|

Presentation:
- 30 tablet pack - 40325111000001108

Administration of Remdesivir

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

Presentation:
- 100mg powder for solution for infusion, 1 vial – 38376311000001103

Administration of Sotrovimab

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

Presentation:

- Sotrovimab 500mg/8ml solution for infusion vials – 40219011000001108

9. Any organisation treating patients admitted due to COVID under this policy with the 2.4g dose casirivimab and imdevimab antibody combination, or prescribing remdesivir to children aged 12-17 years and not on supplementary oxygen, as off-label products, 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.

10. Adhere to the guidance which has been developed by the Specialist Pharmacy Service (SPS) to support the administration of antivirals and monoclonal antibodies.

11. In England, trusts who have not yet done so should register (by site) to participate in COVID-19 specific medicine 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.

12. 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.

13. Organisations should note that initial supply of COVID 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**.

14. 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
    - 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
    - PF-07321332(nirmatrelvir) (150mg tablets) and ritonavir (100mg tablets), 30 tablet pack
    - Remdesivir 100mg powder for concentrate for solution for infusion
    - Sotrovimab 500mg/8ml solution for infusion vials

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 adults, and children aged 12 and above and weighing at least 40kg. 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.

PF-07321332(nirmatrelvir) plus ritonavir (Paxlovid) is a combination oral antiviral supplied by Pfizer that works by inhibiting a protease required for viral replication. It is supplied as a pack providing a five-day treatment course containing both PF-07321332(nirmatrelvir) (150mg tablets) and ritonavir (100mg tablets). PF-07321332(nirmatrelvir) plus ritonavir has a conditional market authorisation in Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)), and a section 174 approval covers use in Northern Ireland, for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.

Remdesivir (Veklury) is supplied by Gilead. Delivered intravenously, it has a conditional market authorisation for use as a treatment for COVID-19 in both Great Britain (under the Medicines and Healthcare products Regulatory Authority (MHRA)) and in Northern Ireland (under the European Medicines Agency (EMA)) for 1) adults, and adolescents aged 12 and over weighing at least 40kg, 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 a conditional marketing authorisation in Great Britain (England, Scotland and Wales) and in Europe (under the European Medicines Agency, covering Northern Ireland) 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 the licensing determination made by the European Medicines Agency.

Off Label Use of the Casirivimab and Imdevimab Combination Antibody and the Antiviral Remdesivir

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. The use of remdesivir for COVID-19 in adolescents aged 12-17 years not yet requiring supplemental oxygen is also off-label. As such, clinicians prescribing either 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

There is no interaction expected of the monoclonal antibodies or antiviral treatments covered under the policy with other treatments available for COVID under published UK clinical access policies - 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. 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.