Public Health Link

From the Chief Medical Officer for Wales

Distribution:	As Appendix 1
From:	Sir Frank Atherton, Chief Medical Officer
Date:	4 January 2022
Reference:	CEM/CMO/2022/02
Category:	Immediate (cascade within 6 hours)
Title:	Neutralising monoclonal antibody and intravenous antiviral treatments for patients in hospital with COVID-19 infection
What is this about:	Further to the interim commissioning policy issued on 16 December, the policy has been updated reflect the RECOVERY trial's announcement of a new sotrovimab arm for patients hospitalised due to COVID and to include a new treatment option of intravenous antiviral therapy (remdesivir (Veklury)) for patients with hospital onset COVID infection..
Why has it been sent:	**For your awareness and to aid signposting patients appropriately.**

Neutralising monoclonal antibody and intravenous antiviral treatments for patients in hospital with COVID-19 infection

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 policy has now been revised following the publication of evidence from the PINETREE trial and the award of a marketing authorisation

variation 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 at the off-label total dose of 2.4g of casirivimab and imdevimab.

Clinicians are encouraged to enter 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.

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.

Action

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 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 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.

[1] An equivalent marketing authorisation variation for Great Britain is currently being considered by the Medicines and Healthcare products Regulatory Authority (MHRA) under the 'reliance model'. Ahead of the MHRA's determination, use of remdesivir under the policy in Great Britain would be considered off-label. 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.

2. Organisations should ensure that anti-s spike antibody testing[2] 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 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 surveillance and enable reimbursement of associated assay costs in England (parallel reimbursement will be available in the other devolved administrations).

3. Genotyping is a key element of the management of inpatients with COVID-19 infection. 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).

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.

   Presentations:
   - Casirivimab 300 mg per 2.5 mL (120 mg/mL) with Imdevimab 300 mg per 2.5 mL (120 mg/mL)
   - Casirivimab 1332 mg per 11.1 mL (120 mg/mL) with Imdevimab 1,332 mg per 11.1 mL (120 mg/mL)
   - Remdesivir 100mg powder for solution for infusion
   - Sotrovimab 500mg/8ml solution for infusion vial

6. Any organisation treating patients under this policy with either the casirivimab and imdevimab antibody combination or with remdesivir, as off-label products, will be required to assure itself that the necessary internal governance arrangements have been completed before the

[2] 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.

medicine is prescribed. These arrangements may be through the health board / trust 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. 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 national procurement lead pharmacist of their intention to participate.

9. 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.

10. 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.

11. Regular stock updates should be provided to Wales' national procurement lead pharmacist and health board/ hospital chief pharmacists when requested. 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

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.

Remdesivir (Veklury) is supplied by Gilead. Delivered intravenously, it has a conditional market authorisation for use as a treatment for COVID-19 in the United Kingdom for adults, and children aged 12 and over weighing at least 40 kg, with pneumonia requiring supplemental oxygen. 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.

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. As such, clinicians prescribing this treatment should follow health board / hospital governance procedures in relation to the prescribing of off-label medicines.

Remdesivir is authorised as a treatment for COVID-19 in the United Kingdom but its use under the published policy is currently off-label. As such, clinicians in Great Britain prescribing this treatment should follow trust / hospital governance procedures in relation to the prescribing of off-label medicines. Use of remdesivir within Northern Ireland is covered by a conditional marketing authorisation determined by the European Medicines Agency but use in patients aged below 18 would be off label. As such, clinicians in Northern Ireland 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

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.

Yours sincerely,

Dr Frank Atherton
Chief Medical Officer

Appendix 1

To: NHS Wales Shared Services Partnership to forward to:

All General Practitioners - please ensure this message is seen by all practice nurses and non-principals working in your practice and retain a copy in your 'locum information pack'.
All Community Pharmacists
Deputising services
HB Chief Pharmacists
HB Prescribing Advisers
Independent/Private clinics and Hospitals and Hospices throughout Wales

To: Health Boards and NHS Trusts:

Chief Executives
Medical Directors
Nurse Directors
Directors of Public Health
Hospital Principals and Chief Pharmacists
Onward distribution to:
Immunisation Leads,
Infectious Disease Departments
Acute medical units
Microbiologists

To: Public Health Wales:

Chief Executive
Director of Public Health Services
Consultants in Communicable Disease Control
Microbiologists
Consultant Epidemiologists
Vaccine Preventable Disease Programme

Cc: NHS Direct Wales
British Medical Association
Royal College of GPs
Royal College of Nursing
Royal College of Midwives
Royal Pharmaceutical Society
Community Pharmacy Wales
Royal College of Paediatrics and Child Health Wales