

Public Health Link

From the Chief Medical Officer for Wales

Distribution:	As Appendix 1
From:	Sir Frank Atherton, Chief Medical Officer
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Category:	Immediate (cascade within 6 hours)
Title:	Antivirals and neutralising monoclonal antibodies (nMABs) in the treatment of hospitalised patients with COVID-19
What is this about:	Further to the interim commissioning policy issued on 4 January, the policy has been updated to take account of recent evidence.
Why has it been sent:	For your awareness and to aid signposting patients appropriately.

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 attached clinical guide.

Further details on supporting evidence and eligibility, together with further guidance, can be found in the published clinical access policies at: [COVID-19 therapies - alerts and advice | All Wales Therapeutics & Toxicology Centre \(awttc.org\)](https://www.awttc.org/COVID-19-therapies-alerts-and-advice)

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 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 testing¹ 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.**
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.
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.
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.

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.

[Oral antivirals – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice](#)

[Neutralising monoclonal antibodies for COVID-19 – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice](#)

11. Health Boards in Wales should notify the All Wales Specialist Procurement Pharmacist of their intention to participate in COVID-19 specific medicine supply arrangements.
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 the treatment that has been given together with the dose and date of administration.

Healthcare professionals are asked to report any suspected adverse reactions (including congenital malformations and or neurodevelopmental delays following treatment during pregnancy) 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.

Enquiries

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.

Yours sincerely,



Sir Frank Atherton
Chief Medical Officer

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