Rapid Policy Statement

Interim Clinical Commissioning Policy: Neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19

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Commissioning position

The proposal is: neutralising monoclonal antibodies (nMABs) are recommended to be available as a treatment option through routine commissioning for non-hospitalised adults and children (aged 12 years and above) with COVID-19 treated in accordance with the criteria set out in this document. Where treatment with an nMAB is contraindicated or not possible, eligible patients may be offered an antiviral as an alternative.

Background

nMABs are synthetic monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing subsequent entry of the virus into the host cell and its replication. This effectively 'neutralises' the virus particle. The following nMAB has conditional marketing authorisation for use in the treatment of COVID-19 in the UK:

- **Casirivimab and imdevimab (Ronapreve®)**: an nMAB combination that binds specifically to two different sites on the spike protein of the SARS-CoV-2 virus particle

Recent evidence suggests that nMABs and oral antivirals significantly improve clinical outcomes in unvaccinated[1] non-hospitalised patients with COVID-19 who are at high risk of progression to severe disease and/or death. Key findings are as follows:

- Casirivimab and imdevimab administered intravenously reduced the composite outcome of hospitalisation or death by 70% (1.0% in the treatment arm vs 3.2% in the placebo arm) and reduced median time to resolution of COVID-19 symptoms by 4

[1] This evidence has only been collected in unvaccinated populations – further research on vaccinated populations is needed.

days in non-hospitalised patients with mild-to-moderate disease (Weinrich et al, 2021).

- Final results from the Phase 3 MOVe-OUT trial show that the oral antiviral molnupiravir resulted in a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29 (6.8% in the molnupiravir group vs 9.7% in the placebo group, p=0.0218).

Marketing authorisation

Casirivimab and imdevimab

Casirivimab and imdevimab delivered intravenously or subcutaneously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in prophylaxis and treatment of acute COVID-19 infection in adults and children aged 12 years and over. Use of casirivimab and imdevimab in Northern Ireland is subject to the conditional marketing authorisation issued by the European Medicines Agency on 12th November 2021 and/or through a Regulation 174 approval for existing stock.

Molnupiravir

Molnupiravir administered orally has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in the treatment of mild to moderate COVID-19 in adults (aged 18 years and over) with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness. Access to molnupiravir in Northern Ireland for this indication is through a Regulation 174 approval ahead of a licensing determination by the European Medicines Agency.

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria. Pre-hospitalised patients are eligible to be considered if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) testing within the last 72 hours

  AND

- Onset of symptoms of COVID-19[2] [3] within the last 7 days[4]

  AND

- A member of a ‘highest’ risk group (as defined in Appendix 1).

The eligible patients as outlined in this policy should initially be considered for treatment with an nMAB (casirivimab and imdevimab). Where an nMAB is contraindicated, not recommended[5] or the administration of an nMAB is not possible patients may be treated with a five-day course of molnupiravir if the onset of symptoms is in the last 5 days.

[2] The following are considered symptoms of COVID-19: feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhoea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum or phlegm, runny nose

[3] For patients who have been symptomatic (within the specified time period) but are no longer symptomatic, clinical judgement should determine suitability for treatment

[4] Patients will need to be within 5 days of symptom onset if being considered for treatment with molnupiravir (where treatment with casirivimab and imdevimab is not possible)

[5] Certain nMABs may not be effective against the Omicron variant of concern. This is subject to further scientific analysis

Patients who have received an nMAB within a post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) trial (such as the PROTECT-V trial) who meet the eligibility criteria of this policy can still receive treatment with an nMAB.

Exclusion criteria

Patients are not eligible for nMAB treatment in the community if they meet any of the following:

- Require hospitalisation for COVID-19
- Require supplemental oxygen
- Children weighing less than 40kg
- Children aged under 12 years[6]

Cautions

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

Casirivimab and imdevimab

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.

Molnupiravir

The most common adverse reactions (≥1% of subjects) reported during treatment and during 14 days after the last dose of were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

COVID-19 vaccines

Casirivimab and imdevimab binds to epitopes on the SARS-CoV-2 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-SARS-CoV-2 monoclonal antibodies. Limited safety data are available from the study HV-2093 where COVID-19 vaccine was permitted, and no safety concerns were identified.

Further information on the timing of COVID-19 vaccination following administration of casirivimab and imdevimab is available at the following sites:

- Liverpool COVID-19 Interactions (covid19-druginteractions.org)

[6] Molnupiravir is only licensed for adults aged 18 years and above.

- Interactions information for COVID-19 vaccines – SPS – Specialist Pharmacy Services

Pregnancy and women of childbearing potential

The community study investigating casirivimab and imdevimab in non-hospitalised patients with mild-to-moderate COVID-19 included pregnant women, although data on outcomes in this cohort are not yet available.

There are no data from the use of molnupiravir in pregnant women. Studies in animals have shown reproductive toxicity. Molnupiravir is **not recommended** during pregnancy. Individuals of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. 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/. Clinicians are advised to refer to the SmPC for molnupiravir for more information on use during pregnancy or lactation.

Dose and administration

Casirivimab and imdevimab

The recommended dose of casirivimab and imdevimab is 1.2g (600mg each of casirivimab and imdevimab) to be administered either as a single intravenous infusion or by subcutaneous injection[7].

- **For intravenous delivery:** 5ml each of casirivimab and imdevimab (120mg/ml, 10ml in total) should be added to a 250ml pre-filled infusion bag containing 0.9% sodium chloride and administered over 30 minutes.
- **For subcutaneous delivery:** Subcutaneous injections should be administered concurrently each at a different injection site: the upper thighs, the upper outer arms, or the abdomen, except for 5 cm around the navel. The waistline should be avoided. When administering the subcutaneous injections, it is recommended that healthcare professionals use different quadrants of the abdomen or upper thighs or upper outer arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. Subcutaneous injections should not be administered into areas where the skin is tender, damaged, bruised, or scarred.

Preparation and administration of casirivimab and imdevimab should be initiated and monitored by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice.

Refer to the Specialist Pharmacy Services institutional readiness document for further information on the handling, reconstitution and administration of the product.

Casirivimab and imdevimab should not be infused concomitantly in the same intravenous line with other medication.

Molnupiravir

[7] No dose adjustment is recommended in patients with renal impairment. The pharmacokinetics of casirivimab and imdevimab have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment.

The recommended dose of molnupiravir is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. Treatment must not be extended beyond 5 days. Molnupiravir should be commenced as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

To reduce the possibility of emerging resistance, patients should be advised to complete the whole course of treatment even if their symptoms improve and/or they feel better.

Co-administration

Corticosteroids

Administration of systemic dexamethasone or hydrocortisone is recommended in the management of patients with severe or critical COVID-19. Corticosteroids are not suggested in non-severe COVID-19 disease. Updated WHO guidance on the use of systemic corticosteroids in the management of COVID-19 can be found here. nMABs should not be regarded as an alternative to corticosteroids.

There is no interaction of casirivimab and imdevimab or molnupiravir with either dexamethasone or hydrocortisone expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 can be found here. There is no interaction of the casirivimab and imdevimab combination or molnupiravir with remdesivir expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

IL-6 inhibitors

The Clinical Commissioning Policies for the use of IL-6 inhibitors in hospitalised patients with COVID-19 who require supplemental oxygen can be found here. There is no interaction of IL-6 inhibitors with casirivimab and imdevimab or molnupiravir expected. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Safety reporting

It is vital that any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

Governance

Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Clinicians are also required to ensure that any data collection requirements are met for the purpose of ongoing surveillance, audit and relevant research around the use of nMABs and antivirals (see ‘Research’ section below).

Clinical outcome reporting

Hospitals managing COVID-19 patients are strongly encouraged to submit data through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN) (https://isaric4c.net/protocols/).

Effective from

This policy will be in effect from 16 December 2021.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy may need amendment and updating if, for instance, new trial data emerges, supply of the drug changes, or a new evidence review is required. A NICE Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of nMABs and/or antivirals for COVID-19 would supersede this policy when completed.

This policy will be reviewed, if required, as further data emerge on the population prevalence of the omicron variant and any impact it may have on the efficacy of COVID-19 therapies.

Surveillance and service evaluation

There is an urgent need to generate more evidence and greater understanding around the use of nMABs and antivirals 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 and antiviral treatment; the impact of nMAB and antiviral treatment in the community and hospital settings on the immune/virologic response and clinical recovery; and the public health sequelae of nMAB and antiviral 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 laboratory where these samples should be retained for sequencing. At present, no further serial sampling is requested for UK Health Security Agency (UKHSA) purposes, however this may change once clinical and infection control guidance in this area has been renewed in line with the latest evidence.

Clinicians must ensure that any additional data collection requirements are met for the purpose of relevant surveillance, audit and evaluation around the use of nMABs and antivirals. It is expected that there will be ongoing monitoring (involving sample collection) of selected patients treated with nMABs and antivirals (led by UKHSA, for instance around the potential generation of new variants), as well as academic research to generate new knowledge around clinical effectiveness and other relevant aspects of public health.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who

share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
Neutralising monoclonal antibody	Synthetic antibodies that bind to a virus and inhibit its ability to infect host cells and replicate
Spike protein	The part of the SARS-CoV-2 virus that binds to the host cell, which then facilitates its entry into the cell

References

1. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19 [published online ahead of print, 2021 Sep 29]. *N Engl J Med*. 2021;NEJMoa2108163. doi:10.1056/NEJMoa2108163

Appendix 1: Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC).

Cohort	Description
Down's syndrome and other genetic disorders	Patients with Down's syndrome and other genetic conditions that might reasonably be expected to reduce immune competence, beyond the primary immune deficiency syndromes
Sickle cell disease	All patients with a diagnosis of sickle cell disease
Patients with a solid cancer	• Active metastatic cancer and active solid cancers (at any stage) • Patients receiving chemotherapy within the last 12 months • Patients receiving radiotherapy within the last 6 months

Patients with a haematologic malignancy	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant
	• Autologous HSCT recipients in the last 12 months
	• Individuals with haematological malignancies who have
	  ○ received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or
	  ○ anti-CD20 monoclonal antibody therapy in the last 12 months
	• Individuals with chronic B-cell lymphoproliferative disorders receiving systemic treatment or radiotherapy within the last 3 months
	• Individuals with chronic B-cell lymphoproliferative disorders with hypogammaglobulinaemia or reduced peripheral B cell counts
	• Individuals with acute leukaemias and clinically aggressive lymphomas who are receiving chemotherapy or within 3 months of completion at the time of vaccination
	• Individuals with haematological malignancies who have received anti-CD38 monoclonal antibody or B-cell maturation agent (BCMA) targeted therapy in the last 6 months
	• Individuals with chronic B-cell lymphoproliferative disorders not otherwise described above

Patients with renal disease	• Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who:

	○ Received B cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], anti-thymocyte globulin) ○ Have an additional substantial risk factor which would in isolation make them eligible for nMABs or oral antivirals ○ Not been vaccinated prior to transplantation • Non-transplant patients who have received a comparable level of immunosuppression • Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression
Patients with liver disease	• Patients with cirrhosis Child's-Pugh class B and C (decompensated liver disease). • Patients with a liver transplant • Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis) • Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease)
Patients with immune-mediated inflammatory disorders (IMID)	• IMID treated with rituximab or other B cell depleting therapy in the last 12 months • IMID with active/unstable disease on corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID with stable disease on either corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate • IMID with stable disease on either corticosteroids, cyclophosphamide, tacrolimus, cyclosporin or mycophenolate. • IMID patients with active/unstable disease including those on biological monotherapy and on combination biologicals with thiopurine or methotrexate
Primary immune deficiencies	• Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Good's syndrome (thymoma plus B-cell deficiency) • Severe Combined Immunodeficiency (SCID) • Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)

	• Primary immunodeficiency associated with impaired type I interferon signalling • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)
HIV/AIDS	• Patients with high levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis • On treatment for HIV with CD4 <350 cells/mm3 and stable on HIV treatment or CD4>350 cells/mm3 and additional risk factors (e.g. age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, those with alcohol-dependence)
Solid organ transplant recipients	All recipients of solid organ transplants not otherwise specified above
Rare neurological conditions	• Multiple sclerosis • Motor neurone disease • Myasthenia gravis • Huntington's disease