Rapid Policy Statement

Interim Clinical Commissioning Policy: Neutralising monoclonal antibodies and intravenous antivirals in the treatment of COVID-19 in hospitalised patients

Publication date: 24 December 2021

Commissioning position

Neutralising monoclonal antibodies or intravenous antivirals are recommended to be available as a treatment option for COVID-19 through routine commissioning for adults and children (aged 12 years and above) patients in hospital with COVID-19 infection in accordance with the criteria set out in this document.

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 nMABs have conditional marketing authorisation (or Regulation 174 emergency use authorisation in Northern Ireland) 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
- **Sotrovimab (Xevudy)**: an nMAB that both blocks viral entry into healthy cells and clears cells infected with SARS-CoV-2

The following intravenous antiviral has conditional marketing authorisation in the UK:

- **Remdesivir:** an adenosine nucleotide prodrug that is metabolised intracellularly to form the pharmacologically active substrate remdesivir triphosphate which inhibits SARS-CoV-2 RNA polymerase and perturbs viral replication

Results from the RECOVERY trial indicate that casirivimab and imdevimab reduced the relative risk of mortality by 20% (24% in the treatment group vs 30% in those who received standard care alone) in hospitalised patients with COVID-19 who had not mounted an

antibody response of their own to the virus (were seronegative[1]) at the time of treatment. Emerging evidence however indicates that the casirivimab and imdevimab combination has significantly decreased efficacy against the Omicron variant of concern (Hoffmann et al, 2021).

Evidence also suggests that nMABs and the intravenous antiviral remdesivir significantly improve clinical outcomes in unvaccinated[2] patients not requiring hospitalisation for COVID-19 who are at high risk of progression to severe disease and/or death. This evidence formed the basis for the conditional marketing authorisations for these products in the treatment of COVID-19 (see Marketing Authorisation section below). Key findings relevant to this policy are as follows:

- Sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression resulted in a relative risk reduction in hospitalisation or death by 85% (Gupta et al, 2021).
- Remdesivir administered intravenously over 3 days to non-hospitalised patients within 7 days of COVID-19 symptom onset and had risk factors for disease progression[3], resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021).

This rapid policy statement outlines the eligibility criteria for the use of nMABs in the treatment of hospitalised patients with COVID-19 in the following settings:

Group 1. Patients hospitalised for acute COVID-19 illness.

Group 2. Patients with hospital-onset COVID-19

Eligibility criteria

Patients must meet all of the eligibility criteria and none of the exclusion criteria under one of the following pathways[4] [5]:

1) Patients hospitalised for acute COVID-19 illness

Hospitalised patients are eligible to be considered for treatment with **casirivimab and imdevimab** if:

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or where a multidisciplinary team (MDT) has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis

  AND

[1] Refers to patients who were negative for serum antibodies against SARS-CoV-2 spike protein (anti-S antibody negative)

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

[3] Risk factors for progression to severe disease included the following: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥30 kg/m2), immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, and sickle cell disease

[4] For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

[5] Clinical judgement should be applied in making treatment decisions, and may be guided by validated decision support tools such as the ISARIC-4C Mortality and Deterioration Scores

- Hospitalised specifically for the management of acute symptoms of COVID-19[6]

  AND

- Negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2[7] (see section on 'Serum antibody status' below)

  AND

- Genotyping confirms the patient is infected with a non-Omicron variant.

> For patients hospitalised with acute COVID-19 illness there are no available nMABs for the Omicron variant. Please see access policies to dexamethasone (CAS alert), remdesivir and IL-6 inhibitors for these patients.
>
> 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 antibody status) into the RECOVERY trial, which is studying sotrovimab vs standard of care.

The following patients are NOT eligible for treatment in Group 1:

- Children weighing less than 40kg
- Children aged under 12 years
- Known hypersensitivity reaction to the active substances or to any of the excipients of casirivimab and imdevimab as listed in the Summary of Product Characteristics

2) Patients with hospital-onset[8] COVID-19

Patients are eligible to be considered for treatment if the initial criteria below are met:

- Hospitalised for indications other than for the management of acute symptoms of COVID-19[9];

  AND

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test within the last 5 days

  AND

- A member of a 'highest' risk group (as defined in Appendix 1)

  OR

  COVID-19 infection presents a material risk of destabilising a pre-existing condition or illness or compromising recovery from surgery or other hospital procedure (as determined by multidisciplinary team [MDT] assessment).

[6] Eligible patients will be acutely ill and admitted specifically to manage symptoms of COVID-19 infection or if COVID-19 infection has been contracted during the hospital stay, symptoms are such that they would have otherwise prompted a hospital admission, independent of the other reasons for the patient's current admission.
[7] The RECOVERY trial population tested patients specifically for anti-S antibodies.
[8] The infection is likely to have been acquired in hospital.
[9] This includes patients admitted to community and mental health hospitals. Where possible patients should be transferred to a suitable facility for treatment with an nMAB.

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **casirivimab and imdevimab** if:

- Genotypeing confirms the patient is infected with a non-Omicron variant

  AND

- Treatment is delivered within 7 days of symptom onset

  AND

- A baseline serum antibody test (anti-S) against SARS-CoV-2 has been taken **prior** to treatment administration (see 'Data collection requirement' section)[10]

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **sotrovimab** if:

- Genotyping confirms the patient is infected with the Omicron variant

  AND

- Treatment is delivered within 5 days of symptom onset

  AND

- A baseline serum antibody test (anti-S) against SARS-CoV-2 has been taken **prior** to treatment administration (see 'Data collection requirement' section)

If the initial criteria for hospital-onset COVID-19 are met patients are eligible to be considered for treatment with **remdesivir** if:

- Genotyping is unavailable

  OR

- There is evidence of clinical deterioration before genotyping results are available

  OR

- An nMAB is contraindicated or otherwise not possible

  OR

- The clinical decision is that an antiviral is the preferred option

  AND

- Treatment is delivered within 7 days of symptom onset

The following patients are not eligible for treatment in Group 2:

- The pattern of clinical presentation indicates that there is recovery rather than risk of deterioration from infection
- Require hospitalisation specifically for the management of acute COVID-19 illness
- New supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Children weighing less than 40kg
- Children aged under 12 years

[10] Patients in Group 2 do NOT need to be seronegative for anti-S antibodies against SARS-CoV-2 to be eligible for initial treatment as specified in this policy.

- Known hypersensitivity reaction to the active substances or to any of the excipients of the products as listed in the respective Summary of Product Characteristics

Clinical decision-making

1) Genotyping is now a core element of the patient pathway in the management of all inpatients with COVID-19.
2) The nMAB of choice in patients with a confirmed non-Omicron infection should be casirivimab and imdevimab.
3) Patients in Group 1 with a confirmed Omicron variant infection are not eligible for treatment with an nMAB unless they are enrolled in a clinical trial.
4) Where there is evidence of clinical improvement in Group 2 patients, no treatment is required in this cohort.
5) In Group 2, where there is evidence of clear clinical deterioration before genotype results are available, patients aged 18 years or over should proceed to receive treatment with remdesivir at the dose specified in this policy. If the patient requires low-flow supplemental oxygen they should be treated according to the UK Clinical Commissioning Policy for remdesivir for patients hospitalised with COVID-19.
6) Patients in Group 2 with a confirmed non-Omicron infection may be eligible for a further 2.4g dose of casirivimab and imdevimab if they continue to deteriorate such that their acute COVID-19 illness requires hospital-based care, providing they fulfil the eligibility criteria for Group 1 above. The serostatus result taken prior to initial treatment with an nMAB will inform eligibility for additional treatment[11].

Genotyping for variants

Genotyping is now a core element of the patient pathway in the management of all inpatients with COVID-19. Samples from patients being considered for treatment with an nMAB should be marked clearly as **"urgent – treatment is variant-dependent".**

Serum antibody status

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.

In immunocompromised groups, very low 'positive' levels of anti-S antibody on a quantitative assay (within the bottom 10% of the assay's positive range) should be interpreted in the context of clinical decision-making and laboratory advice, and a decision to treat may still be made by the MDT on a case-by-case basis. Providers will be required to report anti-S

[11] As those previously treated with an nMAB will be seropositive for anti-S antibodies against SARS-CoV-2, repeat serology need not be performed upon clinical deterioration. Patients who are seronegative on baseline testing will be eligible for treatment.

antibody levels in treated patients, and the corresponding reference range of the local assay, for central monitoring.

In immunodeficient patients on replacement immunoglobulin (intravenous or subcutaneous), the positive detection of anti-S antibodies should be regarded as a 'positive result of unknown significance'. Patients on replacement immunoglobulin testing positive only for anti-S (and negative for anti-N) antibodies should therefore be considered to be seronegative for SARS-CoV-2, and MDT assessment should judge their eligibility for nMAB treatment. Should evidence for passive transmission of anti-N antibodies through replacement immunoglobulin emerge in the future, the detection of anti-N antibodies should also be regarded as a 'positive of unknown significance'.

If there are concerns or questions around laboratory sensitivity or cut-offs these should be discussed in the first instance with local laboratory leads who will have access to comparative and performance data from the External Quality Assessment (EQA) scheme participation.

Dose

1) Patients hospitalised for acute COVID-19 illness

   The recommended dose of casirivimab and imdevimab is 2.4g[12] (1.2g each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion[13]. Patients may only receive one 2.4g dose (1.2g each of casirivimab and imdevimab) during a course of infection.

   Please note that the use of casirivimab and imdevimab in patients hospitalised with COVID-19 at the 2.4g dose is off-label.

2) Patients with hospital-onset COVID-19

   The recommended dose of casirivimab and imdevimab is 1.2g (600mg each of casirivimab and imdevimab) to be administered as a combined single intravenous infusion[14].

   The recommended dose of sotrovimab is 500mg to be administered as a single intravenous infusion[15].

   The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. **Please note that a 3-day course of remdesivir at the dose specified is off-label.**

Administration

Casirivimab and imdevimab

Infusion solutions should be made up according to the following table:

Dose	Active substance	Diluent	Infusion time

[12] This dose for hospitalised patients was recommended by consensus of an expert group, based on available research and other pharmacokinetic data.
[13] 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.
[14] The 1.2g dose may also be delivered via the subcutaneous route; please refer to the SmPC for further information.
[15] No dose adjustment is recommended in patients with renal or hepatic impairment.

2.4g	1.2g (10ml of 120mg/ml) of casirivimab and 1.2g (10ml of 120mg/ml) of imdevimab Total dose volume: 20ml	250mls of 0.9% sodium chloride	30 minutes (minimum)
1.2g	600mg (5ml of 120mg/ml) of casirivimab and 600mg (5ml of 120mg/ml) of imdevimab Total dose volume: 10ml	250mls of 0.9% sodium chloride	30 minutes (minimum)

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

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.

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.

Sotrovimab

8mls of sotrovimab (62.5mg/ml) should be added to a 100ml pre-filled infusion bag containing 0.9% sodium chloride and administered over 30 minutes. Sotrovimab should not be infused concomitantly in the same intravenous line with other medication.

Preparation and administration of sotrovimab 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.

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated.

If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered.

Remdesivir

200mg of remdesivir (day 1 loading dose) and 100mg of remdesivir (days 2 and 3 maintenance doses), should be diluted in either a 250ml or 100ml pre-filled bag of 0.9% sodium chloride solution and infused over a minimum of 30 minutes.

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated.

Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Cautions

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

Casirivimab and imdevimab or sotrovimab are not intended to be used as a substitute for vaccination against COVID-19.

COVID-19 vaccines

Concomitant administration of an nMAB with COVID-19 vaccines has not been studied. Refer to local/national guidelines for vaccine administration and guidance on the risks associated with administration of a SARS-CoV-2 vaccine.

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

- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
- Interactions information for COVID-19 vaccines – SPS – Specialist Pharmacy Services

Pregnancy and women of childbearing potential

Clinicians should refer to the SmPCs for the relevant products for further information on use in pregnancy and women of childbearing potential.

Casirivimab and imdevimab

The RECOVERY trial included women who were pregnant or breastfeeding, and no serious adverse events were reported. The SmPC for casirivimab and imdevimab states that it should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors.

Sotrovimab

There are no data from the use of sotrovimab in pregnant women. The SmPC for sotrovimab states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the foetus.

Remdesivir

There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

Co-administration

There is no interaction expected between nMABs or remdesivir with the drugs listed below. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Corticosteroids

The UK CAS Alert on the use of corticosteroids in patients with COVID-19 can be found here. 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 and antivirals should not be regarded as an alternative to corticosteroids.

Remdesivir

The Clinical Commissioning Policy for the use of remdesivir in hospitalised patients with COVID-19 can be found here.

IL-6 inhibitors

The Clinical Commissioning Policy for the use of IL-6 inhibitors (tocilizumab or sarilumab) in hospitalised patients with COVID-19 who require supplemental oxygen can be found here.

Safety reporting

Any suspected adverse reactions from treatment with the drugs in this policy should be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

Marketing authorisation

Casirivimab and imdevimab

Casirivimab and imdevimab delivered intravenously has conditional marketing authorisation in Great Britain (England, Scotland and Wales) for use in prophylaxis and treatment of acute COVID-19 infection. Access to casirivimab and imdevimab in Northern Ireland for the above indications is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

The use of casirivimab and imdevimab in patients at a dose of 2.4g is off-label, while its use at the 1.2g dose is within the conditional marketing authorisation.

Sotrovimab

Sotrovimab delivered intravenously 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 for the above indication is through a Regulation 174 approval or a licensing determination by the European Medicines Agency.

Remdesivir

Remdesivir delivered intravenously is has conditional marketing authorisation in the UK for treatment of COVID-19 in adults and adolescents (aged 12 years and over and weighing at least 40kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days. Remdesivir use in Northern Ireland is covered by a European Medicines Agency conditional marketing authorisation for 1) the treatment of adults and children aged 12 years and over (and weighing at least 40 kg) with pneumonia requiring supplemental oxygen for a treatment duration of 5-10 days; and 2) the treatment of COVID-19 in adults who do not require supplemental oxygen within 7 days of symptom onset, for a treatment duration of 3 days. Equivalent marketing authorisation variation for Great Britain is currently being considered by the Medicines and Healthcare products Regulatory Authority (MHRA) under the 'reliance route'. **Ahead of MHRA's determination, use or remdesivir under this policy in Great Britain would be considered off-label. In Northern Ireland, use of remdesivir under this policy in children aged 12-17 years would be off-label.**

Governance

Off-label use of medication

Any provider organisation treating patients with off-label products will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

All patients being considered for treatment with nMABs for COVID-19 during their hospital stay should have their baseline serum antibody (anti-S) status measured prior to treatment to enable further evidence generation around the differential impact of treatment based on serology status.

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 evaluation, including of clinical effectiveness, around the use of nMABs (see 'Surveillance and service evaluation' section below).

Clinical outcome reporting

It is vital to be able to monitor the clinical progression of patients treated with nMABs. 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/). In addition, completion of the Blueteq forms (in England) will provide further essential data. Intermittent blood sampling (sparse sampling) may be required to collect serum concentration data. There will be a standard operating procedure circulated on sparse sampling to monitor serum concentration levels with nMAB treatment.

Effective from

This policy will be in effect from the date of publication.

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 casirivimab and imdevimab, sotrovimab or remdesivir for COVID-19 would supersede this policy when completed.

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 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. Further serial sampling for specific patient groups may be requested as part of UKHSA genomic surveillance purposes, or country specific programmes.

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
Anti-S antibody	Antibodies directed against the spike protein of the SARS-CoV-2 virus

References

1. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients [published online ahead of print, 2021 Dec 22]. N Engl J Med. 2021;10.1056/NEJMoa2116846. doi:10.1056/NEJMoa2116846

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3. Hoffmann M, Kruger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralisation – implications for control of the COVID-19 pandemic. Preprint available at: https://www.biorxiv.org/content/10.1101/2021.12.12.472286v1

4. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Preprint available at: https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1

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)[16].

Cohort	Description
Down's syndrome	All patients with Down's syndrome
Patients with a solid cancer	• Active metastatic cancer and active solid cancers (at any stage) • All patients receiving chemotherapy within the last 3 months • Patients receiving group B or C chemotherapy 3-12 months prior (see Appendix 2) • Patients receiving radiotherapy within the last 6 months

Patients with a haematological diseases and stem cell transplant recipients	• Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases)
	• Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases)
	• Individuals with haematological malignancies who have
	  ○ received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or
	  ○ radiotherapy in the last 6 months
	• Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months except patients with chronic phase chronic myeloid leukaemia (CML) in molecular response or first or second line tyrosine kinase inhibitors (TKI).
	• All patients with myeloma (excluding MGUS) or chronic B-cell lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, follicular lymphoma) or myelodysplastic syndrome (MDS) who do not fit the criteria above.
	• All patients with sickle cell disease.
	• Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (e.g. anti-CD20, anti-thymocyte globulin [ATG] and alemtzumab) within the last 12 months.

[16] For paediatric/adolescent patients (aged 12-17 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment

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
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

Appendix 2: Chemotherapy agents (Groups B and C)

Patients currently on or who have received the following chemotherapy regimens (Groups B and C in the table below) in the last 12 months and are considered to be at higher risk of Grade 3/4 febrile neutropenia or lymphopenia.

Group B	Group C
10-50% risk of grade 3/4 febrile neutropenia or lymphopenia	**>50% risk of grade 3/4 febrile neutropenia or lymphopenia**
• Etoposide based regimens • CMF • Irinotecan and Oxaliplatin based regimens • Cabazitaxel • Gemcitabine • Chlorambucil • Temozolomide • Daratumumab • Rituximab • Obinutuzumab • Pentostatin • Proteosome inhibitors • IMIDs • PI3Kinase inhibitors • BTK inhibitors • JAK inhibitors • Venetoclax • Trastuzumab-emtansine • Anthracycline-based regimens • Fluorouracil, epirubicin and cyclophosphamide (FEC) • Methotrexate, vinblastine, adriamycin/doxorubicin, cisplatin (MVAC) • Adriamycin/doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) • Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) • Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) • Liposomal doxorubicin • Taxane – 3-weekly • Nab-paclitaxel • Carboplatin-based regimens • Ifosphamide-based regimens • Bendamustine • Cladrabine • Topotecan • Cyclophosphamide/Fludarabine combinations • Ifosphamide, carboplatin, etoposide (ICE) • Gemcitabine, dexamethasone, cisplatin (GDP) • Isatuximab • Polatuzumab • Acalabrutinib	• All acute myeloid leukaemia/acute lymphocytic regimens • Bleomycin, etoposide and platinum • Highly immunosuppressive chemotherapy (e.g. FluDAP, high dose Methotrexate & Cytarabine) • Trifluradine/ Tipiracil • KTE-X19 • Gilteritinib

• Dexamethasone, cytarabine, cisplatin (DHAP) • Etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP) • Cyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) • Dacarbazine-based regimens • Lomustine • Magalizumab • Brentuximab vedotin • Asparaginase-based regimens	