Group 2 Patients
Neutralising Monoclonal Antibodies and Antivirals for patients *with hospital-onset* COVID-19
Guidance for use in GGC

Contents

Introduction

This guideline describes the treatments available for patients with hospital-onset COVID if they are in high risk groups or where COVID may destabilise a pre-existing condition. Please remember that all patients with COVID-19 are at high risk of venous thromboembolism (VTE) and thromboprophylaxis should be prescribed in all in-patients with suspected or confirmed COVID-19 infection, unless contraindicated. See the GGC thromboprophylaxis in COVID-19 patients guideline for further information.

The treatments described in this guideline are effective if started within the first 5-7 days of COVID-19 infection. Patients must be symptomatic with symptoms attributable to COVID infection but if they have or develop an oxygen requirement, please refer to the Group 1 guideline for guidance on the use of treatments such as dexamethasone, IL-6 inhibitors and Baricitinib.

Antiviral treatments inhibit the development and replication of viruses such as SARS-CoV-2. Neutralising monoclonal antibodies (nMAB) 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.

Recent evidence suggests that antivirals and nMABs given early in the course of infection significantly improve clinical outcomes in patients with COVID-19 who are at high risk of progression to severe disease and/or death. Key findings are as follows:

- Paxlovid™ (nirmatrelvir plus ritonavir)- administered orally as dual antiviral treatment in the EPIC HR trial resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 days of symptom onset) and 88% (within 5 days of symptom onset) compared to placebo in non-hospitalised, high-risk adults with COVID-19. (Hammond et al, 2022). The WHO has made a strong recommendation for the use of nirmatrelvir-ritonavir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022)
- 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, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021). The WHO has made a conditional recommendation for remdesivir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022). The WHO has made a conditional recommendation for remdesivir in patients with severe COVID-19, and a conditional recommendation against remdesivir in patients with critical COVID-19 (WHO, September 2022).
- 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 at day 29 by 85% in the interim analysis of the COMET-ICE trial (Gupta et al, 2021a). Final analysis of this trial shows a relative risk reduction of 79% (Gupta et al, 2021b). This study was done in pre-Omicron COVID-19 variants. There is evidence of reduced in-vitro neutralisation in the Omicron variants and in September 2022, the WHO made a strong recommendation against the use of sotrovimab patients with COVID-19 (WHO, September 2022).

The above products have conditional marketing authorisations for use in the treatment of COVID-19 in the UK as follows.

- Paxlovid™ 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 for:
    - the treatment of COVID-19 in adults and adolescents (at least 4 weeks of age and weighing at least 3kg) 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 days. Up to 10 days treatment may be offered to severely immunocompromised patients.

    - the treatment of COVID-19 in adults and paediatric patients (weighing at least 40 kg)
    - who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 within 7 days of symptom onset, for a treatment duration of 3 days.
- Sotrovimab (Xevudy™) for the treatment of symptomatic adults, and adolescents (aged 12 years and over and weighing at least 40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. **Exceptionally, sotrovimab may be considered where the above antiviral treatments are deemed unsuitable and its use is supported following MDT assessment. In general, within NHS GGC sotrovimab treatment will be reserved for renal dialysis patients only, to be used at the discretion of the clinicians caring for this cohort of patients.**

The decision to initiate antiviral or nMAB must be made by a Consultant and be within the defined criteria.
If a patient does not meet the eligibility criteria and antiviral or nMAB therapy is still felt to be a therapeutic consideration, the Consultant in charge of the patient's care must discuss the case with at least one other Consultant who has expertise in the management of COVID, for example the on call Infectious Diseases or Respiratory Consultant. It may be that a broader MDT discussion is required in complex cases. The summary and outcome of this discussion, along with the names of the clinicians involved in the discussion, must be clearly documented in a clinical note on Portal.

Group 2 Eligibility Criteria

Hospitalised patients with onset of COVID-19 are eligible to be considered for treatment with nMAB or antiviral medicines if:

- They are hospitalised for indications other than for the management of acute symptoms of COVID-19 (including patients admitted to community and mental health hospitals. Where possible patients being considered for intravenous treatment should be transferred to a suitable facility for treatment delivery.)

AND

- SARS-CoV-2 infection is confirmed by polymerase chain reaction (PCR) test or lateral flow test

AND

- Symptomatic with COVID-19 and showing no signs of clinical recovery.
    - 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.

AND

- They are a member of 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)

*In addition to Appendix 1, conditions at risk of progression to severe disease include, but are not limited to the following: elderly, frail, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥30 kg/m^2).

Children aged <18 years in Group 2 may not be considered for treatment with Paxlovid. For paediatric/adolescent patients (aged 4 weeks-16 years inclusive), paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from the treatment.

Available treatment options for eligible patients are:

- **First-line**: Paxlovid™ (nirmatrelvir plus ritonavir) (antiviral)
- **Second-line**: Remdesivir (antiviral)
  Sotrovimab (nMAB) (by exception) following MDT assessment.
  Note: renal dialysis patients may receive treatment with sotrovimab without MDT approval.

Please see appendix 2 for guidance on selection of treatment.

Please note:

- **there are no clinical data to support the above therapies for patients who test positive but are asymptomatic.**
- **Combination treatment with an nMAB and an antiviral is NOT routinely recommended.**
- **Retreatment of recurrent or prolonged infections in an individual patient should be discussed with one of the ID Consultants in normal working hours. Patients who have previously received treatment with an antiviral or nMAB, and who meet the eligibility criteria within this policy, may receive treatment under this policy for a subsequent infective episode, if clinically appropriate.**
- **Paxlovid has significant drug interactions – the interaction checker must be used before prescribing this medication**

Group 2 Exclusion Criteria

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 and adolescents weighing less than 40kg
- 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 (SmPC)..

Paxlovid™ (nirmatrelvir plus ritonavir) Eligibility Criteria

If the general criteria above are met, patients may be considered for treatment with Paxlovid™ if:

- Treatment is commenced within 7 days of symptom onset*
  AND
- The patient does NOT have a history of advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease (eGFR <30ml/min), but note off-label dosing guidance for CKD 4-5 below.
  AND
- Paxlovid™ treatment has been deemed safe following guidance from the appropriate specialty team(s) – see Appendix 2 for NHS GGC Inpatient Pathway and Prescribing Guide. The accompanying National Clinical Guide for treatment with antivirals and nMABs is available at https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103219

Paxlovid™ Additional Exclusion Criteria

- Children aged less than 18 years
- Pregnancy or breastfeeding
- The patient is taking any of the medications listed in Appendix 3. Please contact pharmacy teams if further advice on potential interactions are required or check https://www.covid19-druginteractions.org/checker.

Paxlovid™ Cautions

Paxlovid™ is not recommended for the treatment of patients with advanced decompensated liver cirrhosis or stage 4-5 chronic kidney disease who are not hospitalised. However, off-label, adjusted dosing can be used in stage 4-5 chronic kidney disease patient group and also in dialysis patients after appropriate evaluation and discussion of risks/benefits with the patient – please see dosing section below.

Dose modification in stage 3 chronic kidney disease (eGFR 30-59ml/min) is recommended as per the SmPC – please see dosing section below.

Please refer to the SmPC for Paxlovid™ for detail on special warnings and precautions for use.

Paxlovid™ has a risk of serious adverse reactions due to interactions with other medicinal products (see Appendix 2 for prescribing guidance).

Initiation of Paxlovid™, a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving Paxlovid™, may increase plasma concentrations of medicinal products metabolised by CYP3A. Initiation of medicinal products that inhibit or induce CYP3A may increase or decrease concentrations of Paxlovid™, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening or fatal events from greater exposures of concomitant medicinal products.
- Clinically significant adverse reactions from greater exposures of Paxlovid™.
- Loss of therapeutic effect of Paxlovid™ and possible development of viral resistance.

Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering nirmatrelvir/ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.

Patients should be advised of the possible gastro-intestinal side-effects of treatment with nirmatrelvir/ritonavir (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If nirmatrelvir/ritonavir treatment cannot be tolerated, an alternative treatment can be considered within the options and criteria of this policy. Combination treatment should not be provided unless in the context of a clinical trial.

Remdesivir

If the general criteria above are met, patients may be considered for treatment with remdesivir if:

- Treatment with Paxlovid™is contraindicated or not possible
  AND
- Treatment is commenced within 7 days of symptom onset

Remdesivir Exclusion Criteria

- As noted above for Group 2 Exclusion Criteria plus:
  - eGFR <30ml/min,
  - ALT>5x ULN

Remdesivir Cautions

Please refer to the SmPC for remdesivir for special warnings and precautions for use. Renal and liver function should be monitored carefully during treatment with remdesivir as clinically appropriate.

Remdesivir should be discontinued in patients who develop any of the following:

- ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

For treatment with remdesivir, an individual clinical decision should be made as to whether pre-treatment urea and electrolytes and liver function tests are required based upon whether recent bloods are available or the patient is considered at risk of undiagnosed liver or kidney disease.

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.

For pregnant women please note pregnancy section below.

Sotrovimab Eligibility Criteria

If the general criteria above are met, patients may be considered for treatment with sotrovimab if:

- Clinical judgement deems that an sotrovimab is the preferred option, supported by MDT. Note: renal dialysis patients may receive treatment with sotrovimab without MDT approval.
  AND
- Treatment with remdesivir and Paxlovid™ are both contraindicated or not possible
  AND
- Treatment is commenced within 7 days of symptom onset*

Sotrovimab Additional Exclusion Criteria

- As noted above for Group 2 Exclusion Criteria.

Where possible, all patients being considered for treatment with sotrovimab should have samples taken for serology testing against SARS-CoV-2 prior to treatment. However, serology results are **not** a requirement for treatment with nMABs under the criteria specified in this policy.

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 sotrovimab, if this is deemed the most appropriate treatment option

Sotrovimab Cautions

Please refer to the SmPC for sotrovimab for special warnings and precautions for use.

Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. These 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.

The nMAB therapy is not intended to be used as a substitute for vaccination against COVID-19.

***Please note treatment commencement for Paxlovid™ and sotrovimab beyond 5 days from symptom onset is off-label.**

Paxlovid™ Dosing & Administration

The recommended dose of Paxlovid™ (nirmatrelvir plus ritonavir) is

- 300mg (two 150mg tablets) nirmatrelvir
  with
- 100mg (one 100mg tablet) ritonavir taken together **orally twice daily for 5 days only**. Treatment must not be extended beyond 5 days.

Dose Reduction Stage 3 Chronic Kidney Disease (eGFR 30-59ml/min)

The recommended dose of Paxlovid™ (nirmatrelvir plus ritonavir) is

- 150mg (one 150mg tablet) nirmatrelvir
  with
- 100mg (one 100mg tablet) ritonavir taken together **orally twice daily for 5 days only**. Treatment must not be extended beyond 5 days.

The remaining tablets of nirmatrelvir should be disposed of in accordance with local requirements.

Off-Label Dose Reduction for Stage 4-5 Chronic Kidney Disease and Dialysis

Renal Function	Licensed Dose	Proposed Dose
eGFR < 30 ml/min	Do not use	300mg nirmatrelvir + 100mg ritonavir once daily D1 Followed by 150mg nirmatrelvir + 100mg ritonavir once daily D2-5
Dialysis	Do not use	**Patients ≥ 40kg – to be given after dialysis** 300mg nirmatrelvir + 100mg ritonavir once daily D1 Followed by 150mg nirmatrelvir + 100mg ritonavir once daily D2-5 **Patients < 40kg – to be given after dialysis** 150mg nirmatrelvir + 100mg ritonavir once daily D1, D3, D5 ie every 48h for THREE doses only,

(Reproduced from http://www.covid19-druginteractions.org/prescribing_resources/paxlovid-renal-dosing)

Paxlovid™ should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of onset of symptoms*. Ideally, patients should able to swallow the oral tablets. There is information about off-label use by crushing the tablets here: http://www.covid19-druginteractions.org/prescribing_resources/paxlovid-crushing-tablets.. They may not be suitable in patients where the enteral route is compromised.

Refer to the University of Liverpool COVID-19 Drug Interactions Checker for further information. https://www.covid19-druginteractions.org/checker

A missed dose should be taken as soon as possible and within 8 hours of the scheduled time, and the normal dosing schedule should be resumed. If more than 8 hours has elapsed, the missed dose should not be taken and the treatment should resume according to the normal dosing schedule.

If a patient requires hospital-based care due to severe or critical COVID-19 after starting treatment with nirmatrelvir/ritonavir, the patient should complete the full 5-day treatment course at the discretion of their healthcare provider.

Remdesivir Dosing and Administration

The recommended dose of remdesivir for this cohort (adults and paediatric patients weighing at least 40kg only) is:

- 200mg intravenously on day 1 followed by
- 100mg intravenously on days 2 and 3.

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.

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. See GGC remdesivir treatment flowchart here.

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.

Sotrovimab Dosing and Administration

The recommended **dose of sotrovimab is a single 500 mg intravenous infusion** administered following dilution.

Sotrovimab must be diluted in a single 100mL bag of 0.9% sodium chloride or glucose 5% (do not require to remove an equivalent volume of saline) - total volume 108mL and given over a minimum of 30 minutes via 0.2 micron inline filter.
The SmPC refers to allowing the vials to reach room temperature before use. This is for reasons of patient comfort during administration. If the diluent bag used is at room temperature, there is no need to allow the vial to warm first.

- **Sotrovimab must not be infused concomitantly in the same intravenous line with other medication. Repeat doses should not be administered**.
- Hypersensitivity reactions, including anaphylaxis, have been reported with administration of sotrovimab. 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 sotrovimab. IRRs observed in clinical studies were mostly mild to moderate in severity. The commonly reported signs and symptoms for these reactions are 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.

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. **Paxlovid™ requires particular attention to the detail**

All healthcare professionals are asked to ensure that any patients who receive a COVID-19 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/.

There are no human data on the use of **Paxlovid™** during pregnancy to inform the drug-associated risk of adverse developmental outcomes - women of childbearing potential should avoid becoming pregnant during treatment with Paxlovid™. **Paxlovid™ is not recommended during pregnancy and in women of childbearing potential not using effective contraception**.

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™.

There 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 below, SmPC and RCOG website for further information).

Remdesivir SmPC (Version 22/12/2022):
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of remdesivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures of the major metabolite of remdesivir that were around human therapeutic exposures. Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it.

RCOG Guidance (updated 15/12/2022) https://app.magicapp.org/#/guideline/LqgJ3E

- Remdesivir, an antiviral, may be considered in pregnant women with COVID-19 in community and hospital settings.
- Clinicians should be aware that the fetal risk profile of remdesivir is largely unknown. See SmPC for further information.

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.
Prescribers should discuss contraception post treatment as appropriate, taking into account the ½ life of sotrovimab is ~49 days.

Fertility

There are no human data on the effect of **Paxlovid™** on fertility. No human data on the effect of **nirmatrelvir** on fertility are available. Nirmatrelvir produced no effects on fertility in rats. There are no human data on the effect of **ritonavir** on fertility. Ritonavir produced no effects on fertility in rats.

No human data on the effect of **remdesivir** on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see SmPC). The relevance for humans is unknown.

There are no data on the effects of **sotrovimab** on human male or female fertility. Effects on male and female fertility have not been evaluated in animal studies.

Breast-feeding

It is unknown whether **nirmatrelvir** is excreted in human or animal milk, and the effects of it on the breast-fed newborn/infant, or the effects on milk production. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of **ritonavir** on the breast-fed newborn/infant or the effects of the medicinal product on milk production. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with **Paxlovid™** and for 7 days after the last dose of **Paxlovid™**.

It is unknown whether **remdesivir** is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remedesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

There are no data on the excretion of **sotrovimab** in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known.

Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Maternal IgG is known to be present in human milk.

Co-Administration

Co-administration of **sotrovimab** and **remdesivir** with corticosteroids, and IL6-inhibitors is permitted and no drug-drug interactions are expected. **All potential interactions with Paxlovid™ must be assessed and mitigated prior to initiating treatment.**
For further information please visit the University of Liverpool COVID-19 Drug Interactions website: (https://www.covid19-druginteractions.org/checker).
Sotrovimab should not be regarded as an alternative to corticosteroids.

Other helpful information on the use of nMABs for COVID

Obtaining supply of Paxlovid™, Remdesivir or Sotrovimab

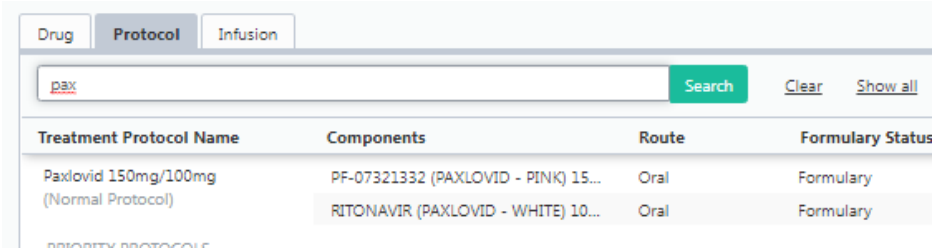
Before prescribing, patients must fulfil the criteria defined above or have approval from a locally arranged MDT if exceptionality applies. **Please ensure interactions with Paxlovid ™ have been checked and mitigated before ordering from pharmacy**.

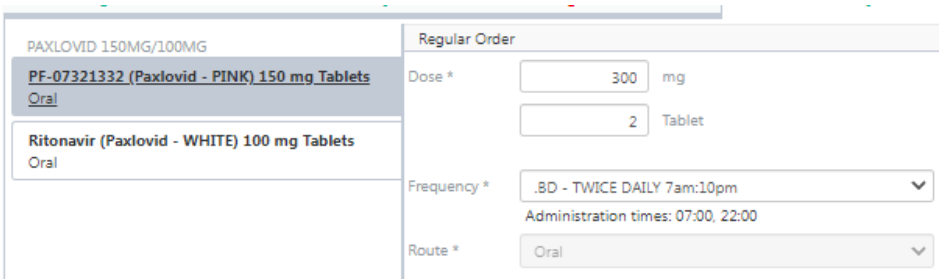
If the one of above medications is indicated, the clinical team looking after the patient should contact the ward clinical pharmacist in first instance to arrange a supply. If no ward pharmacist available, contact main pharmacy for a named-patient supply. The indent should indicate the patient ID details including CHI and which consultant has approved its use. **For Paxlovid™ ensure dose is clearly stated.** Pharmacy departments will supply the remdesivir or sotrovimab vials. For sotrovimab a 0.2 micron inline filter and a worksheet required to assemble the final infusion for administration will also be supplied. **These will be supplied on a named patient basis only during pharmacy opening hours. Please do not contact the on-call pharmacist out of hours for supply**. Sotrovimab must be stored in a fridge when not in use (do not keep inline filters in fridge). Completed worksheets should be filed in the patients notes. Paxlovid™ will be supplied labelled to enable the supply to be taken home with the patient if they are discharged before the 5 day course is complete. If a reduced dose of Paxlovid™ has been requested, supply will be made with excess tablets removed from the packaging.

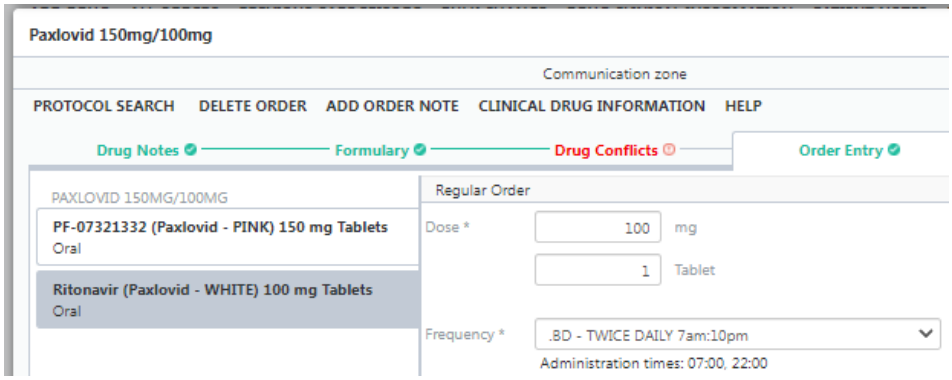
Prescribing & Administering Paxlovid™ on HEPMA

In HEPMA Paxlovid™ has been set up as a 'protocol' for prescribing rather than a 'drug' due to being two physical products that must be prescribed and administered.

Please see screenshots below for the process of selecting the protocol and prescribing (Please ensure correct dose of nirmatrelvir in the case of dose reduction required).







Monitoring, tracking and follow up

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 mention the name of the treatment, that an antiviral or nMAB has been given and the date of administration.

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 treatments; the impact of nMAB and antiviral treatments 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.

Monitoring of longer-term progress is strongly recommended via recruitment of patients receiving COVID therapies to the ISARIC-CCP study.

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

COVID-19 Vaccines

The Green Book states

"Monoclonal antibodies to COVID-19 have recently been licensed for the treatment and prophylaxis of COVID-19 infection. Primate data suggests that administration of the AstraZeneca combination monoclonal antibody product did not interfere with the subsequent response to active vaccination. Based on this limited evidence, therefore, no specific interval is required between receipt of these products and COVID-19 vaccination, or vice versa. As the use of these products is likely to be prioritised to those who are less able to respond to vaccination, for example immunosuppressed individuals, additional doses of vaccine may be required as outlined above"

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040677/Greenbook-chapter-14a-14Dec21.pdf

Appendix 1

Table 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). Please see full Clinical Guide at: https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103219

Clinical Guide: Speciality advice for 'highest-risk' cohorts

Speciality-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of nirmatrelvir/ritonavir) may be found in the table below. Contact your local specialist team for further guidance on issues not covered by this advice.

Cohort	Advice/guidance
Liver disease	Nirmatrelvir/ritonavir should not be administered to patients with advanced decompensated cirrhosis. Such patients can be identified by questioning or review of medical records. Patients should be asked if they have ever been admitted to hospital with liver disease and if they are currently receiving regular ascitic drainage. A positive response is a contraindication to nirmatrelvir/ritonavir. If blood tests are available a bilirubin >50 at any time is a contraindication to nirmatrelvir/ritonavir, if the jaundice is due to liver disease. Patients receiving rifaximin (only used in very advanced liver disease) should not receive nirmatrelvir/ritonavir.
Solid organ transplant (non-renal)	Nirmatrelvir/ritonavir is currently contraindicated in both Solid Organ and Islet Transplant recipients due to significant harmful drug interactions especially anti-rejection medication. These patients should be triaged to receive sotrovimab.
Renal disease (including renal transplant)	Currently nirmatrelvir/ritonavir is not indicated in the majority of at-risk individuals with renal disease, due to lack of dosing information or drug interactions. These include patients with CKD stage 4 and 5, including those on dialysis, and in transplant patients due to interactions with immunosuppressive therapy. Nirmatrelvir/ritonavir requires dose modification in people with CKD stage 3 (see product information). When nMAbs are not indicated or available, clinicians can discuss alternative treatment options such as remdesivir with renal provider clinicians. Remdesivir may be used in patients with an eGFR of ≥30ml/min/1.73m² and in some patients on haemodialysis (discuss with renal clinicians for further guidance).
Solid cancer (including metastases); Haematological disease (including non-malignant conditions)	Specialist cancer and haematology teams are encouraged to establish a central provider email account to receive queries from clinicians treating patients with COVID-19 with antivirals and/or nMABs. For patients who are receiving SACT or complex supportive care for malignancy or stem cell transplantation, please ask whether the patient has already been contacted or reviewed by their specialist haematology/oncology/bone marrow transplant team. If the patient has not already been in contact with their specialist, please establish the location of the provider and consider referral to the respective specialist team via the central provider email where available. Please ask the patient to have details of their current medication available for any following consultation.
Rare neurological conditions	There are no specific needs for specialist neurology services to prescribe nirmatrelvir/ritonavir, though care should be taken with those who have difficulty swallowing or have supported feeding, and for those with behavioural or psychiatric concerns. If a patient is identified as eligible for nirmatrelvir/ritonavir due to neurology risk factors then ask about swallowing difficulties. Disease-specific advice is as follows: **Multiple Sclerosis (MS)** • In addition to the medicines listed in the SPS guidance, avoid concurrent use of nirmatrelvir/ritonavir with the following: siponimod, cladribine and modafinil • For those patients taking oral or intravenous methylprednisolone discuss the steroid dose with the MS neurology team as nirmatrelvir/ritonavir may increase corticosteroid levels. **Myasthenia Gravis** • This includes muscle specific kinase (MUSK) myasthenia and the Lambert-Eaton Myasthenic Syndrome (LEMS). There are anecdotal reports of myasthenia gravis worsening in association with nirmatrelvir/ritonavir • There are no known specific drug interactions. Myasthenia can be aggravated by COVID-19 and COVID-19 vaccination and requires close monitoring given the risk of bulbar and respiratory failure. **Motor Neurone Disease (MND)** • Discuss patients on quinine with an MND physician • Levels of riluzole treatment may be increased by nirmatrelvir/ritonavir and should be temporarily suspended following discussion with an MND physician. **Huntington's Disease** • In addition to the medicines listed in the SPS guidance, avoid concurrent use of nirmatrelvir/ritonavir with the following: primidone, tetrabenazine and trihexyphenidyl
Immunology	Considering commonly prescribed medications in immunology, there are no issues with concomitant immunoglobulin replacement therapy and nirmatrelvir/ritonavir and nMABs. Patients should be informed by specialist clinicians and clinical/patient networks to maintain a list of all medications including those prescribed in hospital. Patients may be taking prophylactic antimicrobials - please refer to the list of contraindicated medications in the SPS guidance for further reference.
Obstetrics and gynaecology	It is recommended that CMDU staff liaise with their Maternity COVID Champion, or dedicated clinician when assessing a pregnant patient with COVID. Please ensure that a full drug history and past medical history is taken as other specialists may also need to be involved, for example renal or transplant teams. 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 nirmatrelvir/ritonavir.
Paediatrics	For paediatric/adolescent patients, paediatric multidisciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from treatment.

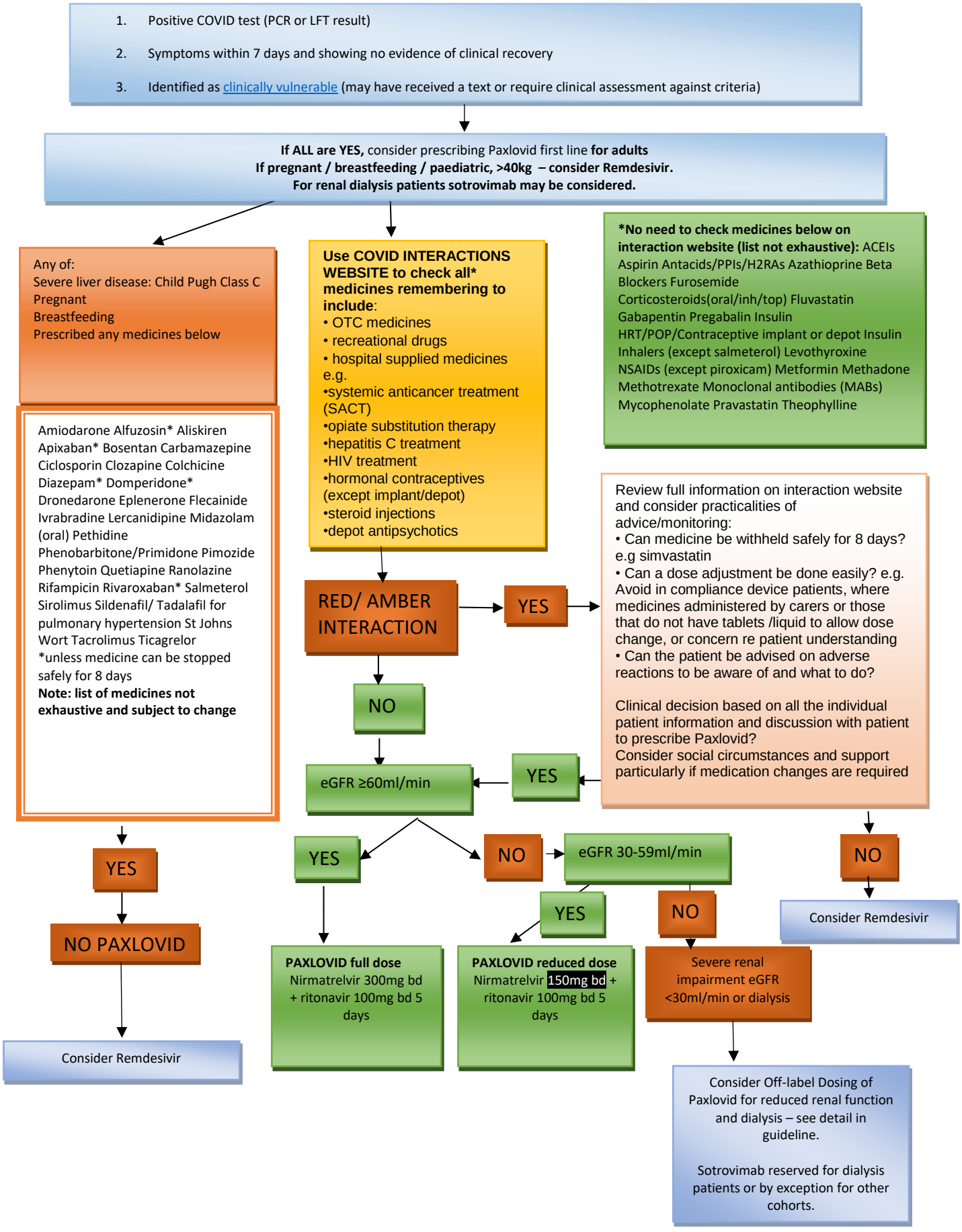
Clinical Guide: Speciality advice for 'highest-risk' cohorts

Speciality-specific advice on the management of patients within each of the highest-risk cohorts (particularly around the use of nirmatrelvir/ritonavir) may be found in the table below. Contact your local specialist team for further guidance on issues not covered by this advice.

Cohort	Advice/guidance
IMID	**Factors to be considered in IMID patients**: • Consistent with existing guidance on management of COVID-19 in patients with IMID, patients should temporarily suspend their conventional DMARD(s), biologic and/or JAK inhibitor until the course of antiviral treatment has been completed and symptoms of COVID-19 are improving (this will usually be between 1-3 weeks). For most patients this will not require specific contact with the specialty team. • Do not stop or decrease corticosteroids • Swallowing difficulties may preclude the use of oral antivirals e.g. in patients with dysphagia due to myositis, oesophageal dysmotility due to scleroderma/systemic sclerosis because of the size of the tablets (approximately 2cm long) • Do not delay antiviral treatment pending specialist advice The following links on speciality websites may be useful: • The British Society for Rheumatology website • COVID-19 guidance | British Society for Rheumatology • COVID-19 Guidance & Advice - The British Society of Gastroenterology (bsg.org.uk) • British Thoracic Society website: https://www.brit-thoracic.org.uk/covid-19/ • British Association of Dermatologists Advice for Dermatology HCPs during COVID-19 pandemic: https://www.bad.org.uk/healthcare-professionals/covid-19
HIV/AIDS	• It is recommended that each CMDU has details of their local HIV specialist service (both specialist HIV pharmacist and HIV physician) to discuss individuals where advice is needed. Speciality arrangements for referral to HIV specialist advice may be regional in some areas. • The majority of individuals living with HIV and referred to CMDUs for nirmatrelvir/ritonavir treatment should be managed in accordance with the guidance without the need for referral to the specialist centre. There are no antiretroviral treatment (ART) regimens that are a contraindication to nirmatrelvir/ritonavir treatment. No dose adjustment of any ART agent including ritonavir or cobicistat is needed. Interactions with other generalist co-medications prescribed should be assessed according to guidance including by reference to the Liverpool Covid drug interaction website. • Some individuals living with HIV do not disclose their HIV status to their GPs. It is therefore good practice to enquire of individuals during triage if they have any other medical conditions or take any other medications not managed directly by their GP. • CD4 counts are no longer routinely monitored in those with virological suppression and previous counts above 350 cells/mm3. These individuals will generally be assessed as not meeting the immunosuppression criteria although some patients may still meet the criteria that take account of other demographic factors and co-morbidities. We suggest using an age threshold of 55 years or older as an appropriate indicator for treatment in these circumstances as this was the inclusion criteria used in clinical studies.

Down's syndrome[1]	• The following issues should be given due consideration when assessing a patient for treatment with a suitable antiviral or nMAB:
	  • The individual is likely to have impaired ability to understand the information given and they may be more likely to have hearing and communication difficulties
	  • There is significant potential for co-existence of significant health conditions
	  • There is a need for a corroborated and detailed collateral medical and drug history from an informant
	  • Mental capacity assessment is an essential part of the assessment/triage process in these individuals
	  • Other people cannot consent for an individual's treatment unless they are legally permitted to do so
	  • In patients iudged not to have capacity, a process of best interests decision-making should be pursued.
	• A person with Down's syndrome may be more likely to be taking medications that are contra-indicated or which may lead to interactions with nirmatrelvir/ritonavir e.g.:
	  • For heart conditions and high blood pressure
	  • Antipsychotics, antidepressants, anxiolytics
	  • Anticonvulsants (anti-epileptics)
	  • Statins
	• Nirmatrelvir/ritonavir tablets are relatively large (8-9mm diameter) and should not be crushed. Patients with swallowing difficulties will need support to ensure these are taken safely.
	• Contact the hospital learning disability liaison nurse (if available) or the local specialist learning disability service for clinical advice around psychotropic medications and the implication of contraindications and potential interactions

Appendix 2 In-Patient Pathway in NHS GGC and Prescribing Guidance



COVID-19
CLINICAL GUIDELINE

Note: This guideline has been fast-tracked for approval for use within NHSGGC

Covid-19 Group 2 Patients Neutralising Monoclonal Antibodies and Antivirals for patients with hospital-onset COVID-19

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

Version Number:	5
Does this version include changes to clinical advice:	Yes
Date Approved:	4th January 2023
Approval Group:	**NHSGGC Covid-19 Tactical Group (Acute)**

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.