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 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

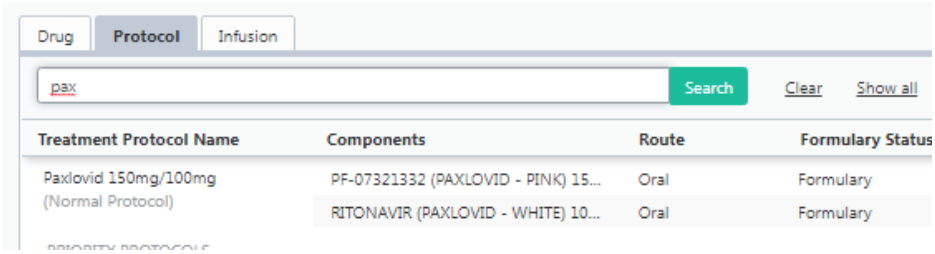
Before prescribing, patients must fulfil the criteria defined above or have approval from a locally arranged MDT if exceptionality applies. **Please ensure interactions with Paxlovid ™ have been checked and mitigated before ordering from pharmacy**.

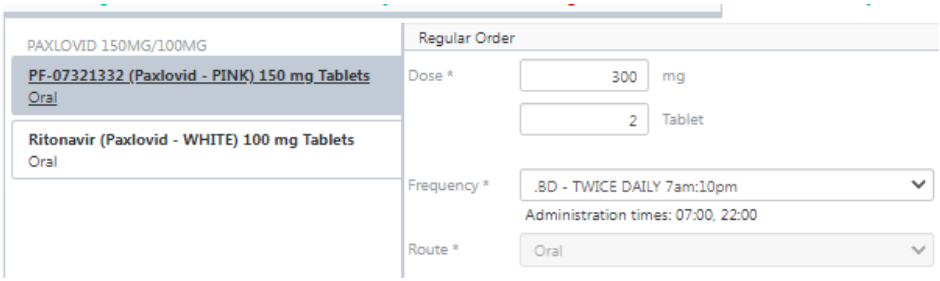
If the one of above medications is indicated, the clinical team looking after the patient should contact the ward clinical pharmacist in first instance to arrange a supply. If no ward pharmacist available, contact main pharmacy for a named-patient supply. The indent should indicate the patient ID details 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.

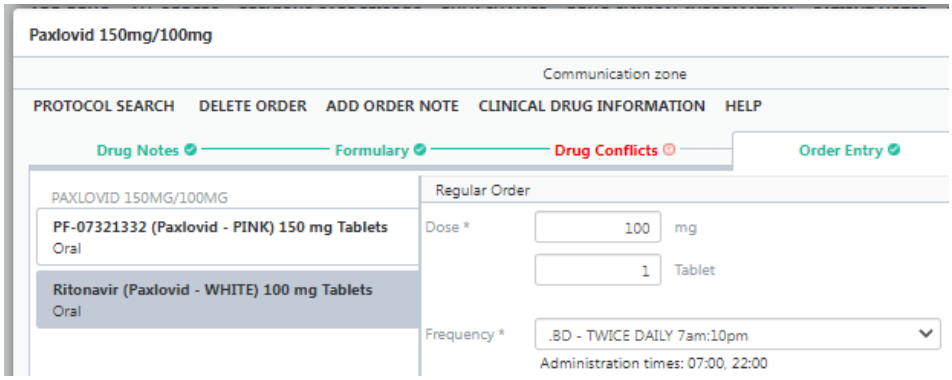
Prescribing & Administering Paxlovid™ on HEPMA

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

The following patient cohorts were determined by an independent advisory group commissioned by the Department of Health and Social Care (DHSC). Please see full independent advisory group report at: https://www.gov.uk/government/publications/higher-risk-patients-eligible-for-covid-19-treatments-independent-advisory-group-report-march-2023

Box 1 Risk factors for progression to severe COVID-19 in adults

Risk factors for progression to severe COVID-19 in adults defined by the independent advisory group commissioned by the Department of Health and Social Care (June 2023)

Down's syndrome and other genetic disorders

All individuals with Down's syndrome or other chromosomal disorders known to affect immune competence

Solid cancer

- metastatic or locally advanced inoperable cancer
- lung cancer (at any stage)
- people receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy within 12 months
- people who have had cancer resected within 3 months and who received no adjuvant chemotherapy or radiotherapy
- people who have had cancer resected within 3 to 12 months and receiving no adjuvant chemotherapy or radiotherapy are expected to be at less risk (and thus less priority) but still at increased risk compared with the non-cancer populations

Haematological diseases and recipients of haematological stem cell transplant (HSCT)

- allogeneic HSCT recipients in the last 12 months or active graft versus 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 CAR-T cell therapy in the last 24 months, or until the lymphocyte count is within the normal range
- individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months, or radiotherapy in the last 12 months
- all people who do not fit the criteria above, and are diagnosed with:
    - myeloma (excluding monoclonal gammopathy of undetermined significance [MGUS])
    - AL amyloidosis
    - chronic B-cell lymphoproliferative disorders (chronic lymphocytic leukaemia, follicular lymphoma)
    - myelodysplastic syndrome (MDS)
    - chronic myelomonocytic leukaemia (CMML)
    - myelofibrosis
    - any mature T-cell malignancy
- all people with sickle cell disease
- people with thalassaemia or rare inherited anaemia with any of the following:
    - severe cardiac iron overload (T2 * less than 10 ms)
    - severe to moderate iron overload (T2 * greater than or equal to 10 ms) plus an additional comorbidity of concern (for example, diabetes, chronic liver disease or severe hepatic iron load on MRI)
- individuals with non-malignant haematological disorders (for example, aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (for example, anti-CD20, anti-thymocyte globulin [ATG] and alemtuzumab) within the last 12 months

Renal disease

- renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who have:
  - received B-cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], ATG)
  - an additional substantial risk factor which would in isolation make them eligible for monoclonals or oral antivirals
- non-transplant renal patients who have received a comparable level of immunosuppression
- patients with chronic kidney disease (CKD) stage 4 or 5 (an estimated glomerular filtration rate [eGFR] less than 30 ml per min per 1.73 m^2) without immunosuppression

Liver diseases

- people with cirrhosis Child-Pugh (CP) class A, B and C, whether receiving immune suppressive therapy or not. Those with decompensated liver disease (CP B and C) are at greatest risk
- people with a liver transplant
- people with liver disease on immune suppressive therapy (including people with and without cirrhosis)

Solid organ transplant recipients

Solid organ transplant recipients not in any of the above categories

Immune-mediated inflammatory disorders (diseases in which autoimmune or autoinflammation-based pathways are implicated in disease, for example, inflammatory arthritis, connective tissue diseases, inflammatory skin diseases, inflammatory gastrointestinal disease)

- people who have received a B-cell depleting therapy (anti-CD20 drug, for example, rituximab, ocrelizumab, ofatumab, obinutuzumab) in the last 12 months
- people who have been treated with cyclophosphamide (IV or oral) in the 6 months prior to positive PCR or relevant COVID test
- people who are on corticosteroids (equivalent to or greater than 10 mg per day of prednisolone) for at least the 28 days prior to positive PCR
- people who are on biologics or small molecule JAK inhibitors
- people who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine, mercaptopurine, or similar agents (for major organ involvement such as kidney, gastro-intestinal tract, liver, lung, brain), methotrexate (for interstitial lung disease or asthma only) and/or ciclosporin. No minimum dose threshold is suggested
- people who are on current treatment (or within the last 6 months) with S1P modulators (fingolimod, ponesimod or siponimod), or alemtuzumab or cladribine within the last 12 months
- people who exhibit at least one of: (a) uncontrolled or clinically active disease (that is, required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR); and/or (b) other high risk comorbidities (for example, body mass index [BMI] greater than 30, diabetes mellitus, hypertension, major organ involvement such as significant kidney, liver, nervous system or lung inflammation or significantly impaired renal, liver, nervous system and/or lung function)

Respiratory

- asthma in people on oral corticosteroids (defined above). Any asthma patient taking immunosuppressants for their asthma including but not exclusively methotrexate, ciclosporin
- COPD on long term home non-invasive ventilation (NIV). Patients on long term oxygen therapy. People with moderate or severe disease (FEV1 less than or equal to 50% predicted) who have required 4 or more courses of prednisolone 30 mg for 5 days or greater in last 12 months
- interstitial lung disease (ILD) – all patients with idiopathic pulmonary fibrosis
- sub-types of ILD, for example, connective tissue disease related, sarcoidosis, hypersensitivity pneumonitis, NSIP (non-specific interstitial pneumonia) who have received a B-cell depleting therapy in last 12 months, or IV or oral cyclophosphamide in the 6 months prior to testing positive for COVID-19. Any ILD patient on current treatment with corticosteroids, mycophenolate mofetil, azathioprine, tacrolimus, cyclosporin or methotrexate. No minimum dose criteria

- any people with any type of ILD who may not be on treatment due to intolerance but has severe disease with an FVC predicted less than 60%
- NIV and tracheostomy ventilated – all patients requiring this type of support regardless of the underlying disorder (which might include COPD, obesity hypoventilation syndrome, scoliosis, bronchiectasis, neurodisability and genetic muscular diseases [refer to neurology section]).
- lung cancer patients, refer to 'Solid cancer' section above
- lung transplant patients (refer to solid organ transplant section)
- pulmonary hypertension (PH): groups 1 and 4 from PH classification

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 or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- primary immunodeficiency associated with impaired type 1 interferon signalling
- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)
- any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy

HIV/AIDS

- people with high levels of immune suppression, have uncontrolled or untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis
- people on treatment for HIV with CD4 less than 350 cells per mm3 and stable on HIV treatment or CD4 greater than 350 cells per mm3 and additional risk factors (for example, age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, alcoholic dependency)

Neurological disorders

- Conditions associated with neuromuscular respiratory failure requiring chronic ventilatory support:
  - motor neurone disease
  - Duchenne muscular dystrophy
- Conditions that require use of specific immunotherapies:
  - multiple sclerosis (MS)
  - myasthenia gravis (MG)
  - other immune-mediated disorders
- Dementia, neurodegenerative and neuroimmune disorders when associated with severe frailty (for example, levels 7 or 8 on Clinical Frailty Scale, as part of a personalised care plan):
  - Alzheimer's disease, vascular disease, Lewy body disease, or frontotemporal atrophy
  - Parkinson's disease
  - Huntington's disease
  - progressive supranuclear palsy and multiple system atrophy
  - motor neurone disease
  - multiple sclerosis and other immune-mediated neurological disorders

Box 2 Risk factors for progression to severe COVID-19 in young people aged 12 to 17 years

Pathway for PCR positive symptomatic cases aged older than 12 and younger than 18 years, greater than 40 kg weight, and clinical concern: defined by the independent advisory group commissioned by the Department of Health and Social Care (March 2023)

Non-hospitalised individuals in the older than 12 and younger than 18 years age range considered at high risk from COVID-19 and to be prioritised for consideration of treatment with neutralising monoclonal antibodies when symptomatic and SARS-CoV-2 PCR positive. Concerned clinicians should refer for regional multidisciplinary team (MDT) case discussion through local established pathways, who will confirm eligibility and consider risk benefit and whether to proceed with offer of treatment.

Children and young people (CYP) at substantial risk

Complex life-limiting neurodisability with recurrent respiratory infections or compromise.

CYP at significant risk if 2 or more of these risk factors are present

Primary immunodeficiency:

- common variable immunodeficiency (CVID)
- primary antibody deficiency on immunoglobulin (or eligible for immunoglobulin replacement)
- hyper-IgM syndromes
- Good's syndrome (thymoma plus B-cell deficiency)
- severe combined immunodeficiency (SCID)
- autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- primary immunodeficiency associated with impaired type 1 interferon signalling
- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)

Secondary immunodeficiency:

- HIV CD4 count less than 200 cells per mm3
- solid organ transplant
- haematological stem cell transplant (HSCT) within 12 months, or with graft versus host disease (GVHD)
- CAR-T cell therapy in last 24 months
- induction chemotherapy for acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphoma, chemotherapy for acute myeloid leukaemia (AML), relapsed and/or refractory leukaemia or lymphoma

Immunosuppressive treatment:

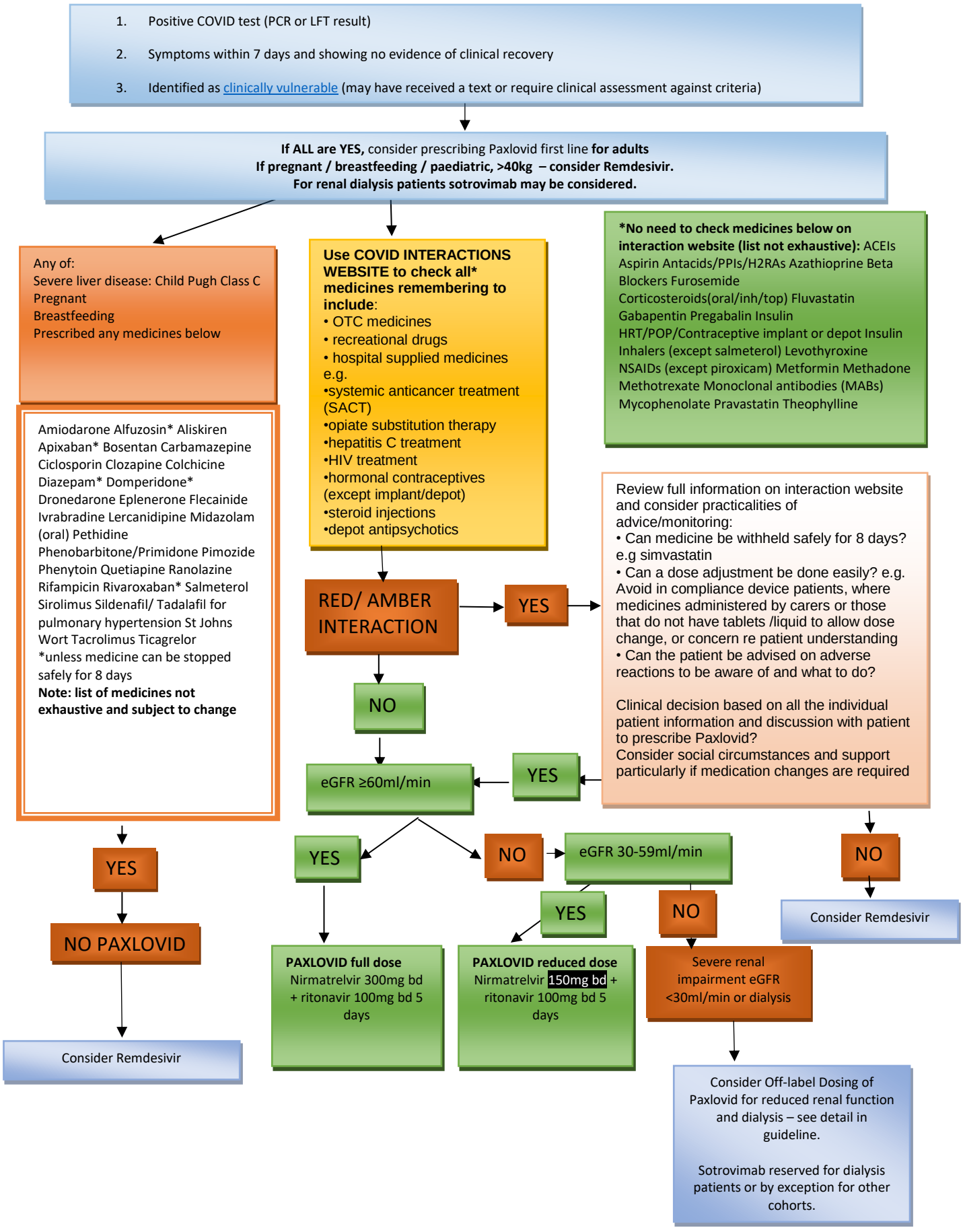
- chemotherapy within the last 3 months
- cyclophosphamide within the last 3 months
- corticosteroids greater than 2 mg per kg per day for 28 days in last 4 weeks
- B-cell depleting treatment in the last 12 months

Other conditions:

- high body mass index (BMI; greater than 95th centile)
- severe respiratory disease (for example, cystic fibrosis or bronchiectasis with FEV1 less than 60%)
- tracheostomy or long-term ventilation
- severe asthma (paediatric intensive care unit [PICU] admission in 12 months)
- neurodisability and/or neurodevelopmental disorders
- severe cardiac disease
- severe chronic kidney disease
- severe liver disease
- sickle cell disease or other severe haemoglobinopathy
- trisomy 21
- complex or chromosomal genetic or metabolic conditions associated with significant comorbidity
- multiple congenital anomalies associated with significant comorbidity

- bronchopulmonary dysplasia – decisions should be made taking into account degree of prematurity at birth and chronological age
- infants less than 1 year with congenital heart disease (CHD):
    - cyanotic CHD
    - haemodynamically significant acyanotic CHD and history of prematurity
    - those due for corrective surgery, to avoid complications or delay due to SARS-CoV-2 infection

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



Document History

Version	Date	Description
1.0	18/11/2021	Evolution of previous Ronapreve guidance v1.1 from 01/11/2021 Approval of First Release after MHRA Ronapreve CAS Alert 04/11/2021
2.0	22/12/2021	Review after MHRA CAS Alert 08/12/2021 & 16/12/2021
3.0	19/01/2022	Review after MHRA CAS Alert 24/12/2021
4.0	16/02/2022	Review after MHRA CAS Alert 27/01/2022
5.0	06/10/2022	Review after MHRA CAS Alert 24/02/2022 & 30/05/2022 update high risk cohorts
6.0	29/12/2022	Review after MHRA CAS Alert 28/11/2022
7.0	09/01/2024	Routine review; update high risk cohorts as per NICE TA878 22/06/2023; document history added

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:	6
Does this version include changes to clinical advice:	Yes
Date Approved:	31st January 2024
Approval Group:	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.