Treatment of hospital-onset COVID-19 in adults and children

Antiviral medications inhibit viral replication and prevent progression of infection. Neutralising monoclonal antibodies (nMABs) are synthetic monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing subsequent entry of the virus into the host cell and its replication. This effectively 'neutralises' the virus particle.

The following products are licensed for use in patients with COVID-19 who do not require supplemental oxygen but are at high risk of progression to severe COVID19 (please refer to the current Summary of Product Characteristics (SmPCs) for further details of the individual marketing authorisations):

- **Antivirals**
  - Nirmatrelvir plus ritonavir (Paxlovid®)
  - Remdesivir
  - molnupiravir
- **nMABs**
  - Sotrovimab (Xevudy®)

The Scottish Medicines Consortium (SMC) collaborated with National Institute for Health and Care Excellence (NICE) on the Multiple Technology Appraisals (MTA) 878, which includes positive treatment recommendations for the following licensed COVID-19 treatments relevant to this guideline; nirmatrelvir plus ritonavir (Paxlovid®) and sotrovimab (Xevudy®). The recommendations are also applicable to NHS Scotland.

Final MTA treatment recommendations for molnupiravir (Lagevrio®) and remdesivir (Veklury®) are unlikely to be available until later in 2023 as they are subject to appeal. In the meantime, NICE's COVID-19 rapid guideline covers the use of these medicines.

1. Patient selection

Group 1 Patients hospitalised **for** acute COVID-19 illness	There currently are **NO** nMABs suitable as a treatment option in Group 1 patients. Please continue to consider one or more of corticosteroids, remdesivir, tocilizumab, baricitinib for these patients where clinically appropriate as per the current access protocols. Where patients are ineligible for treatment under this policy, recruitment to the RECOVERY trial should be considered.
Group 2 Patients with **hospital-onset** COVID-19	Aim of treatment in group 2 is to prevent destabilising an existing condition or clinical deterioration of COVID -19, therefore treatment should be given at the earliest opportunity where clinically appropriate. Refer to the detailed policy for access criteria and the treatment options in this patient group

The following policy details treatment options for **Group 2 patients only**.

2. Allowed Prescribers

Antivirals (nirmatrelvir/ritonavir (Paxlovid®); OR remdesivir OR molnupiravir) or an nMAB (sotrovimab) for the treatment of COVID-19:

- must only be initiated by a Consultant.
- must be prescribed on the Hospital Electronic Prescribing & Medicine Administration system
- must be prescribed on an Infusion Therapy Recording Chart (remdesivir or sotrovimab only)

3. Eligibility criteria for Group 2 patients

Patients with hospital onset COVID-19 are eligible to be considered for **one** of the treatment options if **all** of the initial criteria are met:

3.1 Initial access criteria

- Hospitalised for indications other than for the management of acute symptoms of COVID-19 [1];

AND

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

AND

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

AND

- Do not require supplemental oxygen for COVID-19.

AND

- Has increased risk for progression to severe COVID-19, as defined in the independent advisory group report commissioned by the Department of Health. Further advice may be required from the speciality who manages this condition(s) for the patient.

[1] *This includes 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*

3.2 Exclusion criteria

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

- Require hospital-level care for the management of acute COVID-19 illness
- 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)

3.3 Treatment choice

Eligible patients may be considered for treatment with **one** of the following:

First-line	Nirmatrelvir/ ritonavir (Paxlovid®) (antiviral - oral)
Alternative treatment options	Sotrovimab (nMAB – intravenous infusion) Remdesivir (antiviral – intravenous infusion) Molnupiravir (antiviral – oral) – to be discussed with pharmacist if all of the above options not suitable and refer to ADTC 390 for access criteria and information on dosing, supplies etc.

- Combination treatment with an nMAB and an antiviral is **NOT** routinely recommended
- Patients who have previously received treatment with an nMAB or antiviral and who meet the eligibility criteria above may receive a repeat course for a subsequent infective episode, if clinically appropriate.

Children and adolescents

- Eligible children and adolescents may **only** be considered for treatment with remdesivir (weighing 40kg and above) or sotrovimab (for those aged 12 years and above AND weighing 40kg and above).
  - a national paediatric multi-disciplinary team (MDT) assessment is required to determine clinical capacity to benefit from the treatment, so contact should be made with the Duty Paediatrician to discuss. Additional criteria for this patient group can be found in the independent advisory group report commissioned by the Department of Health

If the initial criteria for hospital-onset COVID-19 are met, patients are eligible to be considered for **one** of the following treatment options where all the additional criteria and none of the additional exclusion criteria are met:

Medicine choice	
Nirmatrelvir/ ritonavir (Paxlovid®) ***First line***	**Additional access criteria** • Treatment is commenced within 5 days of symptom onset
	Additional exclusion criteria • under 18 years of age • pregnancy • severe hepatic impairment • stage 4-5 chronic kidney disease (CKD) • patient is taking any medications-contra-indicated with nirmatrelvir/ ritonavir (Paxlovid®) (table 1 in SmPC and see section 3.4 below for further information) **Cautions** • refer to the SmPC for special warnings and precautions for use. • nirmatrelvir/ ritonavir (Paxlovid®) has a risk of serious adverse reactions due to interactions with other medicinal products (see table 2 in SmPC and section 3.4 below on drug interactions below for additional information). • Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution

	should be exercised when administering Paxlovid® to patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis.
Alternative treatment options	
Sotrovimab	**Additional access criteria** • Treatment is delivered within 5 days of symptom onset **AND** • Nirmatrelvir/ ritonavir (Paxlovid®) is contraindicated or unsuitable
	Additional exclusion criteria • under 12 years of age • aged 12-17 years weighing less than 40kg • refer to the SmPC for special warnings and precautions for use.
Remdesivir	**Additional access criteria** • Treatment is commenced within 7 days of symptom onset **AND** • Treatment with nirmatrelvir/ritonavir (Paxlovid®) is contraindicated or unsuitable *NICE COVID-19 rapid guideline: Managing COVID-19 (published 29 March 2023), advises when assessing the person, take into account their likely response to any vaccinations already given, any comorbidities or risk factors, and whether their condition is deteriorating.*
	Additional exclusion criteria • children and young people weighing less than 40kg • Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (except in patients with end-stage renal disease on haemodialysis – discuss with Renal Team) • Baseline alanine transaminase (ALT) ≥5 times the upper limit of normal • Co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended • refer to the SmPC for special warnings and precautions for use 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). 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. If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of

	remdesivir as per ADTC 357: remdesivir for patients hospitalised due to COVID-19.
Molnupiravir	This can be considered if all of the above are not suitable. Refer to ADTC 390: Treatments for Highest Risk Non-Hospitalised Patients (adults and children) with COVID-19 for further information on the use of molnupiravir.

3.4 Drug Interactions

- No interactions between sotrovimab or remdesivir with corticosteroids (dexamethasone or hydrocortisone), remdesivir or IL-6 inhibitors (e.g. tocilizumab) are expected.
- Further information on interactions can be found within the SmPCs of the relevant products or via the University of Liverpool COVID-19 Drug Interactions website.

Additional information for nirmatrelvir/ritonavir (Paxlovid®)

- Initiation of nirmatrelvir/ritonavir (Paxlovid®), a CYP3A inhibitor, in patients receiving medicinal products metabolised by CYP3A or initiation of medicinal products metabolised by CYP3A in patients already receiving nirmatrelvir/ ritonavir (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 nirmatrelvir/ ritonavir 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 (nirmatrelvir/ ritonavir (Paxlovid®).
  - Loss of therapeutic effect of nirmatrelvir/ritonavir (Paxlovid®) and possible development of viral resistance.
- A number of useful resources can be accessed to provide further guidance on these interaction and their management:
  - SmPC for nirmatrelvir/ritonavir (Paxlovid®)
  - University of Liverpool COVID-19 Drug Interactions website and their Prescribing Resources, which includes a guide on assessing a patient for treatment with Paxlovid®.

3.5 COVID-19 vaccines

nMABs (e.g. sotrovimab) are not intended to be used as a substitute for vaccination against COVID-19.

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

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

- Liverpool COVID-19 Interactions (covid19-druginteractions.org)
- COVID-19: the green book, chapter 14a. UK Health Security Agency

4. Pregnancy, breastfeeding, use in women of childbearing potential and effect on fertility

In **all** cases of pregnancy and breastfeeding, senior Obstetric advice should be sought to ensure that theoretical risks to the fetus (or baby in the case of breastfeeding) do not outweigh proven benefits to the mother. In some cases of breastfeeding, it may be more appropriate to seek advice from a pediatrician.

Clinicians should refer to the SmPCs of the relevant products for further information on their use in pregnancy, breast feeding, women of childbearing potential and effects on fertility.

In addition the current guidance from the Royal College of Obstetricians and Gynaecologists on Coronavirus (COVID-19), infection in pregnancy should be followed.

All healthcare professionals are asked to ensure that any patients who receive a COVID-19 antiviral (e.g. Paxlovid®) 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 https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry.

Nirmatrelvir/ritonavir (Paxlovid®)

- There are no human data on its use 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 are no human data on the use of Paxlovid® in 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. Breast-feeding should be discontinued during treatment with Paxlovid® and for 7 days after the last dose of Paxlovid®.

Sotrovimab

- There are no data from its use 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.
- 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**.**

Remdesivir

- There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (see SmPC for further information).
- Women of child-bearing potential have to use effective contraception during treatment.
- It is unknown whether remdesivir is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production. 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.

5. Dosing schedules and administration information for medicines recommended for Group 2 patients

5.1 Nirmatrelvir/ ritonavir (Paxlovid®)	
Dose	Recommended dose of nirmatrelvir/ritonavir (Paxlovid®) is 300mg (two 150mg tablets) nirmatrelvir with 100mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. In patients with **moderate renal impairment (CKD stage 3),** the dose of nirmatrelvir/ritonavir should be reduced to nirmatrelvir 150 mg (one 150mg tablet) with 100 mg (one 100mg tablet) ritonavir taken together orally twice daily for 5 days. The remaining 150mg tablet of nirmatrelvir should be disposed of in accordance with local requirements.
Supplies	A treatment course of Paxlovid® will be supplied from the pharmacy department. A limited supply for use outwith pharmacy opening hours will also be available from: • University Hospital Ayr - Emergency Drug cupboard • University Hospital Crosshouse – Emergency Drug cupboard • Arran War Memorial Hospital • Lady Margaret Hospital, Millport
Administration	Paxlovid® should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of onset of symptoms. Clinicians should assure themselves that patients are able to swallow the oral tablets. Refer to the University of Liverpool COVID-19 Drug Interactions Checker for further information on administration to patients with swallowing problems. Note these recommendations may be *off-label, refer to the NHS Ayrshire & Arran Code of Practice for Medicines Governance Section 9 (b) "Off-label use of medicines" for further information.* Patients should be advised of the possible gastro-intestinal side-effects of treatment with Paxlovid® (e.g. nausea, vomiting). If such side-effects are experienced, anti-emetics should be considered that are not contra-indicated. If Paxlovid® treatment cannot be tolerated, an alternative treatment can be considered within the options and criteria of this policy. Combination treatment should not be provided. 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 Paxlovid®, the patient should complete the full 5-day treatment course at the discretion of their consultant.

5.2 Sotrovimab	
Dose	Recommended dose of **sotrovimab** is 500mg to be administered as a **single** intravenous infusion No dose adjustment is recommended in elderly patients or those with renal or hepatic impairment.
Supplies	Sotrovimab will be supplied from the pharmacy department. A limited supply of sotrovimab and pre-assembled consumable kits will also be available from: • University Hospital Ayr - Emergency Drug cupboard • University Hospital Crosshouse – Emergency Drug cupboard • Arran War Memorial Hospital • Lady Margaret Hospital, Millport
Preparation	Sotrovimab requires to be prepared in clinical areas. Sotrovimab and pre-assembled consumables kit with a worksheet to prepare the infusion will be supplied from the pharmacy department. Completed worksheets must be filed in the patient's notes. For further information refer to the drug monograph within the Medusa Injectable Medicines Guide available on AthenA.
Administration	• The recommended dose should be administered as a single intravenous infusion and be given over 30 minutes via a 0.2micron in-line filter using an infusion pump. • Resuscitation and anaphylaxis treatment facilities must be readily available during and for 1 hour after the end of the infusion. • Sotrovimab should only be administered during daytime hours • For further information refer to the drug monograph within the Medusa Injectable Medicines Guide for administration instructions.
Monitoring	Hypersensitivity reactions, including serious and/or life-threatening reactions such as anaphylaxis, have been reported following infusion of sotrovimab. Hypersensitivity reactions typically occur within 24 hours of infusion. Signs and symptoms of these reactions may include nausea, chills, dizziness (or syncope), rash, urticaria and flushing. If signs and symptoms of severe hypersensitivity reactions occur, administration should be discontinued immediately and appropriate treatment and/or supportive care should be initiated. If mild to moderate hypersensitivity reactions occur, slowing or stopping the infusion along with appropriate supportive care should be considered. **Baseline observations** should be recorded using the current NEWS (National Early Warning Score) chart (or a PEWS chart if being used in paediatric patients) and repeated every 15 minutes during the infusion and then every 30 minutes until 1 hour post infusion. Note that hypersensitivity reactions can occur during or within 24 hours of the infusion and patients should be advised to report any signs.

5.3 Remdesivir	
Dose	Recommended dose of **remdesivir** for this patient cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days of symptom onset. If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as per ADTC 357: remdesivir in patients hospitalised due to COVID-19.
Supplies	Remdesivir will be supplied from the pharmacy department. A limited supply of remdesivir will also be available from: • University Hospital Ayr - Emergency Drug cupboard • University Hospital Crosshouse – Emergency Drug cupboard • Arran War Memorial Hospital • Lady Margaret Hospital, Millport
Preparation	• Remdesivir requires to be prepared in clinical areas • refer to the drug monograph within the Medusa Injectable Medicines Guide for details on preparation.
Administration	• Resuscitation and anaphylaxis treatment facilities must be readily available during the infusion. • Remdesivir should only be administered during daytime hours Refer to the drug monograph within the Medusa Injectable Medicines Guide for administration and monitoring instructions.
Monitoring	• 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. **Baseline observations** should be recorded using the current NEWS (National Early Warning Score) chart (or a PEWS chart if being used in paediatric patients) and repeated every 15 minutes during the infusion and then every 30 minutes until a minimum of 30 minutes post infusion (this may be extended based on clinical judgement). • 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). • If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as per ADTC 357: remdesivir in patients hospitalised due to COVID-19.

6. Adverse effects

- Refer to the monitoring within sections 5.2 and 5.3.
- Also refer to the cautions section (3.3 and 3.4) for nirmatrelvir/ ritonavir (Paxlovid®) specifically for details of interactions which may lead to adverse effects.
- Refer to the SmPCs of the relevant products for further information on adverse effects.

7. Safety reporting

Any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) from any of the treatments should be reported directly to the MHRA via the dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

It should be noted that Paxlovid®, sotrovimab, and remdesivir are all black triangle medicines.

8. Communication

All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) should explicitly record that if an antiviral or nMAB has been given along with the dose and date of administration.

9. Bibliography

1. CEM/CMO(2023)001. COVID Therapeutic Alert 2023 1 – Publication of NICE Multiple Technology Appraisal (MTA) – Treatment recommendation for COVID-19, Available from: COVID therapeutic alert 2023 1 – publication of NICE multiple technology appraisal (MTA) – treatment recommendations for COVID-19 (scot.nhs.uk) (accessed 07 April 2023).
2. Scottish Medicines Consortium, SMC 2557 nirmatrelvir and ritonavir (Paxlovid®) 150mg and 100mg film coated tablets, issued 29 March 2023, updated 06 April 2023. Nirmatrelvir and ritonavir (Paxlovid) (scottishmedicines.org.uk) (accessed 07 April 2023).
3. Scottish Medicines Consortium, SMC 2555 Sotrovimab (Xevudy®) 500mg concentrate for solution for infusion issued 29 March 2023, updated 06 April 2023. Sotrovimab (Xevudy) (scottishmedicines.org.uk) (accessed 07 April 2023).
4. Department of Health & Social Care. Independent report- Defining the highest-risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs (updated March 2023): independent advisory group report Published 05 April 2023. Available from Defining the highest risk clinical subgroups upon community infection with SARS-CoV-2 when considering the use of neutralising monoclonal antibodies (nMABs) and antiviral drugs (updated March 2023) - GOV.UK (www.gov.uk) (accessed 07 April 2023).
5. National Institute for Clinical Excellence (NICE). Multiple Technology Appraisal (MTA) TA878: casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19, published updated 29 March 2023, updated 05 April 2023. Available from:

Overview | Casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 | Guidance | NICE (accessed 07 April 2023).

6. NICE guideline [NG191]. COVID-19 rapid guideline: managing COVID-19. Published: 23 March 2021. Last updated: 29 March 2023. Available from: Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE (accessed 07 April 2023).
7. RCOG, Royal College of Midwives, Royal College of Paediatrics and Child Health, Public Health England and Public Health Scotland. Coronavirus (COVID-19), infection in pregnancy, Version 16.0: updated Thursday 15 December 2022. Available from: Coronavirus (COVID-19), infection in pregnancy | RCOG (accessed 07 April 2023).
8. Paxlovid® (nirmatrelvir/ritonavir) 150 mg/100 mg film-coated tablets. Summary of Product Characteristics, last updated on eMC 20 October 2022. Available from: https://www.medicines.org.uk/emc/product/13145 (accessed 07 April 2023).
9. Xevudy® (sotrovimab) 500 mg concentrate for solution for infusion Summary of Product Characteristics, last updated on eMC 05 January 2023. Available from https://www.medicines.org.uk/emc/product/13097 (accessed 07 April 2023).
10. Veklury® (remdesivir) 100 mg powder for concentrate for solution for infusion Summary of Product Characteristics, last updated on eMC 24 January 2023. Available from https://www.medicines.org.uk/emc/product/11597 (accessed 07 April 2023).
11. NHS Specialist Pharmacy Service. Getting ready to use sotrovimab: guidance for Chief Pharmacists. Published 14 December 2021. Last updated 1 December 2022 Available from: Getting ready to use sotrovimab: guidance for Chief Pharmacists – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice (accessed 07 April 2023).